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# Vascular Effects, Angiotensin I-Converting Enzyme (ACE)-Inhibitory Activity, and Antihypertensive Properties of Peptides Derived from Egg White

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In this study, we have identified novel antihypertensive peptides derived from egg-white proteins. The sequences YRGGLEPINF and ESIINF produced an acute blood-pressure-lowering effect in spontaneously hypertensive rats upon a single oral administration. Our results suggest that the antihypertensive action could be attributed to a vascular-relaxing mechanism that would occur *in vivo* independently of angiotensin I-converting enzyme (ACE) inhibition, because neither these peptides nor their main digestion fragments, except for the dipeptide YR, acted as ACE inhibitors *in vitro*. The vasodilator and antihypertensive activity of the sequences ESI and NF would explain the blood-pressure-lowering effect of ESIINF. With regard to YRGGLEPINF, in addition to NF, YR appeared as the main fragment responsible for its activity. The dipeptide YR, named kyotorphin and previously identified as an endogenous analgesic neuropeptide in the central nervous system, showed strong vasodilator and antihypertensive properties. The structure–activity features of the vasodilator peptides are discussed.

**KEYWORDS: Egg white hydrolysate; ACE-inhibitory activity; vasodilator properties; bioactive peptides; antihypertensive activity**

## INTRODUCTION

Regulatory peptides can be released by enzymatic hydrolysis of food proteins and may act as potential physiological modulators. Among these, antihypertensive peptides are the focus of major attention in view of the prevalence and importance of hypertension. Several antihypertensive peptides have been identified in hydrolysates of various protein sources, such as casein, whey proteins, chicken, fish, soy, or egg (*1–5*). Furthermore, studies have been performed with certain antihypertensive food peptides on human patients that have clinically proven their health benefits (*6–10*).

The search for angiotensin I-converting enzyme (ACE) inhibitory activity is the most common strategy followed in the selection of antihypertensive peptides (*11*). The classical approach involves the *in vitro* determination of the ACE-inhibitory activity of food protein hydrolysates obtained by enzymatic digestion or microbial fermentation, followed by the identification of peptide structures and the chemical synthesis of potentially active peptides or their analogues, to confirm their activity. The *in vivo* effects are usually tested in spontaneously hypertensive rats (SHR), which constitute an accepted model for human essential hypertension. In many cases, the results of those tests have highlighted a lack of correlation between the *in vitro* ACE-inhibitory activity and the *in vivo* action (*12*). This is probably because, when the selection of potential antihypertensive substances is solely based on the *in vitro* determination of the ACE-inhibitory activity, important aspects, such as the physiological transformations that determine the bioavailability of the peptides or the existence of other mechanisms of action, are overlooked (*13*).

In fact, antihypertensive food peptides with mechanisms of action other than ACE inhibition, such as those possessing antioxidant, vasodilator, and opioid activities, have been reported (*14–17*). In this context, certain egg-white-derived peptides and synthetic analogues play a role in controlling hypertension by exerting non-ACE-mediated vasodilator effects (*18–20*). In previous studies, we showed that egg white hydrolysed with pepsin (hEW) inhibited ACE *in vitro* and exhibited antihypertensive effects in SHR (*21–24*). Indeed, the effect on arterial

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blood pressure caused by hEW was traced to the *in vivo* inhibition of ACE in tissues, such as the aorta and kidney (*25*). Furthermore, some of the peptide sequences contained in hEW that acted as ACE inhibitors *in vitro* were identified (*21*). Nevertheless, the whole hydrolysate and some of the peptides included therein also exhibited other activities, such as antioxidant (*26*) and vascular-relaxing activity (*27, 28*), that could contribute to the antihypertensive effect.

The aim of this study was to characterize novel peptides derived from egg white with antihypertensive activity. For this purpose, we screened the effects of sequences devoid of ACE-inhibitory activity, previously identified in hEW, on the vascular function of rat isolated aorta. The blood-pressure-lowering effect of the peptides with vasodilator activity was checked in SHR. Finally, the gastrointestinal digestion of the antihypertensive peptides was simulated, in an attempt to identify the fragments responsible for the *in vivo* action.

## MATERIALS AND METHODS

**Drugs and Synthetic Peptides.** Phenylephrine, acetylcholine, and captopril were purchased from Sigma Chemical Co. (St. Louis, MO). We used the following synthetic peptides, previously identified in egg white hydrolysed with pepsin, devoid of ACE-inhibitory activity *in vitro* (*21*): VALDGGL (ovotransferrin 392–398), SALAM (ovalbumin 36–40), RDILNQ (ovalbumin 84–89), FSL (ovalbumin 99–101), YRGGLEPINF (ovalbumin 125–134), ELIN (ovalbumin 144–147), YQIGL (ovalbumin 212–216), VLLPDEVSGL (ovalbumin 243–252), ESIINF (ovalbumin 256–261), and DGSRQPV (ovotransferrin 230–236). The fragments resulting from the simulation of the gastrointestinal digestion of YRGGLEPINF and ESIINF (YRGGLEPI, YR, GGLEPI, ESI, and NF) were also synthesized. All of these peptides were obtained by conventional Fmoc solid-phase synthesis with a 431A peptide synthesizer (Applied Biosystem, Inc., Überlingen, Germany) according to the method described by Atherton and Sheppard (*29*). They were synthesized and provided by the Unitat de Pèptids of Barcelona University, and their purity (>90%) was verified in our laboratory by reversed-phase high-performance liquid chromatography–tandem mass spectrometry (RP-HPLC–MS/MS) (*30*). The drugs and the peptides were dissolved in distilled water for the reactivity experiments and administration to the rats.

**Simulated Gastrointestinal Digestion.** The two-stage hydrolysis process was carried out according to the method of Alting et al. (*31*). Aqueous solutions (2 mmol/L) of the synthetic peptides YRGGLEPINF and ESIINF were first hydrolysed with pepsin (EC 3.4.4.1; 1:60 000, 3400 units/mg) (Sigma) (enzyme/substrate ratio of 1:50, w/w) for 90 min at 37 °C and pH 2.0, followed by hydrolysis with corolase PP (enzyme/substrate ratio of 1:50, w/w, Röhm, Darmstadt, Germany) at pH 7–8 and 37 °C for 240 min. Corolase PP is a proteolytic enzyme preparation from the pig pancreas gland that, in addition to trypsin and chymotrypsin, contains numerous amino and carboxypeptidase activities. Hydrolyses were carried out in a thermally controlled incubator under continuous stirring (Unitron, Infors AG, Bottmingen, Switzerland). The reaction was stopped by heating at 95 °C for 10 min in a water bath, followed by cooling to room temperature. Each sample was stored at −20 °C until further analysis.

**Analysis by Online RP-HPLC–MS/MS.** Identification of the peptides produced in the simulated gastrointestinal digestion of the sequences YRGGLEPINF and ESIINF was performed on an Agilent HPLC system (Agilent Technologies, Waldbronn, Germany) connected online to an Esquire-LC quadrupole ion-trap instrument (Bruker Daltonik GmbH, Bremen, Germany). The HPLC was equipped with a quaternary-gradient pumping system, an inline degasser, a variable wavelength absorbance detector set at 220 nm, and an automatic injector (all 1100 series, Agilent Technologies, Waldbronn, Germany). The column used in these experiments was a Widepore $C_{18}$ column (250 × 4.6 mm i.d., 5 μm particle size) (Bio-Rad, Richmond, CA). The injection volume was 50 μL. Solvent A was 0.37 mL/L of trifluoroacetic acid (TFA) in milli-Q water, and solvent B was 0.27 mL/L of TFA in acetonitrile. Peptides were eluted with a linear gradient of solvent B in A, from 2 to 10% in 15 min, 10 to 20% in 35 min, and 20 to 30% in 20 min. The flow rate was 0.8 mL/min. The flow was split postdetector by placing a T-piece (Valco, Houston, TX) connected with a 75 μm i.d. peek outlet tube of an adjusted length to give approximately 20 μL/min of flow directed into the mass spectrometer via the electrospray interface. Nitrogen was used as a nebulizing and drying gas and operated with an estimated helium pressure of $5 \times 10^{-3}$ bar. The capillary was held at 4 kV. Spectra were recorded over the mass/charge (*m*/*z*) range of 100–1500. About 25 spectra were averaged in the MS analyses, and about 5 spectra in the MS(n) analyses. The signal threshold to perform auto MS(n) analyses was 5000, and the precursor ions were isolated within a range of 4.0 *m*/*z* and fragmented with a voltage ramp going from 0.35 to 1.4 V. Using data analysis (version 3.0; Bruker Daltoniks), the *m*/*z* spectral data were processed and transformed to spectra representing mass values. BioTools (version 2.1; Bruker Daltoniks) was used to process the MS(n) spectra and perform peptide sequencing.

**ACE-Inhibitory Activity.** ACE-inhibitory activity of the peptides was measured *in vitro* following the spectrophotometric assay described by Cushman and Cheung (*32*), with some modifications as explained below. The substrate, hippuryl-histidil-leucine (HHL), and ACE from rabbit lung (EC 3.4.15.1) were purchased from Sigma. Testing solutions (40 μL) were incubated with 100 μL of 0.1 mol/L borate buffer (pH 8.3) containing 5 mmol/L HHL and 0.3 mol/L NaCl and with 20 μL of ACE (2 mU) at 37 °C for 30 min. The reaction was stopped with 150 μL of 1 mol/L HCl. The hippuric acid formed was extracted with ethyl-acetate (1000 μL) and centrifuged at 1500*g* for 10 min, and 750 μL of the organic phase was evaporated. The residue was dissolved in 800 μL of distilled water, and the absorbance was measured at 228 nm. Triplicate tests were performed for each sample. Inhibitory activity was expressed as the concentration needed to inhibit 50% of ACE activity ($IC_{50}$).

**Experimental Procedure in Rat Aorta.** Three-month old male Sprague–Dawley (SD) rats weighing 250–300 g were used for reactivity experiments. These animals were obtained from the Animals Quarters of Facultad de Medicina of the Universidad Autónoma de Madrid, Spain. They were euthanized by decapitation, and the thoracic aorta was removed and placed in Krebs–Henseleit solution (KHS: 115 mmol/L NaCl, 25 mmol/L $NaHCO_3$, 4.7 mmol/L KCl, 1.2 mmol/L $MgSO_4 \cdot 7H_2O$, 2.5 mmol/L $CaCl_2$, 1.2 mmol/L $KH_2PO_4$, and 11.1 mmol/L glucose) at 4 °C.

Segments of thoracic aorta (3 mm in length), free of fat and connective tissue, were mounted between two steel hooks in isolated tissue chambers containing KHS at 37 °C and continuously bubbled with a 95% $O_2$/5% $CO_2$ mixture, which gave a pH of 7.4. An optimal resting tension of 1.5 g was applied to all aortic segments. This tension was adjusted every 15 min during a 45 min equilibration period before adding drugs. The isometric tension was recorded by using an isometric force displacement transducer connected to an acquisition system (MacLab 8/S, ADInstruments Pty Ltd., Castle Hill, Australia).

After an equilibration period, segments were initially exposed twice to 75 mmol/L KCl to test their functionality and its maximum contractility. The presence of endothelium was confirmed by the relaxation to 10 μmol/L acetylcholine of segments contracted with phenylephrine at a concentration that produces close to 50% of the contraction induced by 75 mmol/L KCl. A relaxation equal to or greater than 80% was considered as evidence of the functional integrity of the endothelium, and the absence of relaxation induced by acetylcholine was considered as evidence of the absence of endothelium.

After 60 min of washout, the relaxation produced by a single concentration (0.1 mmol/L) of the following peptide sequences: VLLPDEVSGL, ELIN, YQIGL, VALDGGL, SALAM, FSL, DGSRQPV, ESIINF, YRGGLEPINF, RDILNQ, YRGGLEPI, GGLEPI, ESI, NF, and YR were studied in segments contracted with phenylephrine, at a concentration that produces a contraction close to 50% of the contraction induced by 75 mmol/L KCl. Results are expressed as means ± standard error of the mean (SEM) of the number of rats indicated in each case.

**Experimental Procedure in Hypertensive Rats.** Male SHR, 17–20 weeks old, weighing 250–300 g (Charles River Laboratories, Barcelona, Spain) were used in this study. The rats remained at a temperature of

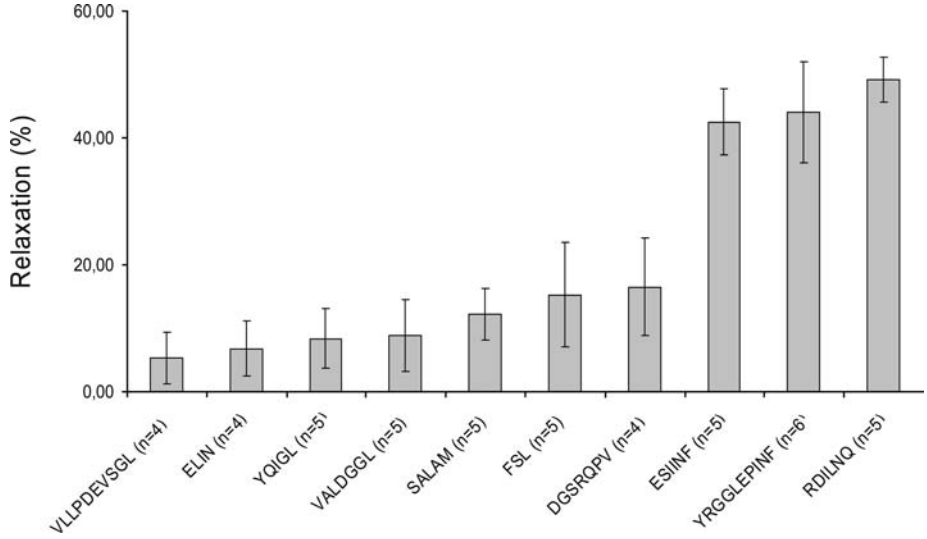


**Figure 1.** Relaxation induced by a single concentration (0.1 mmol/L) of the following peptides: VLLPDEVSGL, YRGGLEPINF, VALDGGL, DGSRQPV, RDILNQ, ESIINF, SALAM, YQIGL, ELIN, and FSL in aortic segments of SD rats. Results (mean ± SEM) are expressed as the relaxation percentage of the contraction previously induced by phenylephrine. The number of animals is shown in the figure.

23 °C with 12 h light/dark cycles and consumed tap water and a standard diet for rats (A04 Panlab, Barcelona, Spain) ad libitum, during the experiments. The sequences YRGGLEPINF, RDILNQ ESIINF, YRGGLEPI, GGLEPI, ESI, NF, and YR were orally administered to these animals (10 mg/kg) by gastric intubation, between 9 and 10 a.m. Captopril (50 mg/kg) and distilled water were used, respectively, as positive and negative controls. All of the products were administered in 1 mL of water. The systolic blood pressure (SBP) of the rats was measured by the tail cuff method (*33*), before the administration and also 2, 4, 6, 8, and 24 h postadministration using a Niprem 645 equipment (Cibertec, Madrid, Spain). Before the measurement, the rats were kept at 37 °C for 10 min to make the pulsations of the tail artery detectable. To guarantee the reliability of the measurements, the rats were accustomed to the procedure 2 weeks before beginning the experiments. Changes in SBP were calculated as the difference between the mean values of six measurements obtained before and after the administration. The results are expressed as mean values ± SEM for a minimum of five rats. The differences were analyzed by one- or two-way analysis of variance (ANOVA) using the GraphPad Prism4 software, followed by the Bonferroni test, and were considered significant when $p < 0.05$.

The investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institutes of Health (NIH Publications 85-23, revised 1996) and complies with the current Spanish and European laws (RD 223/88 MAPA and 609/86).

## RESULTS

**Vasodilator and Antihypertensive Properties of the Egg-White-Derived Peptides. Figure 1** shows the relaxation caused by the peptides derived from the pepsin digest of egg-white proteins, whose vasodilator properties were screened in SD rat aortic segments. We found peptides with a high vasodilator activity that relaxed more than 40% of the contraction caused by phenylephrine in endothelium-intact aorta preparations (YRGGLEPINF, RDILNQ, and ESIINF) and peptides with a low vasodilator activity (SALAM, FSL, DGSRQPV, VLLPDEVSGL, VALDGGL, YQIGL, and ELIN) that produced a relaxation varying from approximately 5 to 17%.

We next investigated whether the sequences with the highest vasodilator activity (YRGGLEPINF, RDILNQ, and ESIINF) produced antihypertensive affects after a single oral administration to SHR. The results are shown in **Figure 2**. Before the administration of the different products, the SHR showed SBP values of 172 ± 2.8 mmHg ($n = 15$) that did not change with the administration of distilled water ($p > 0.05$ by one-way ANOVA). In agreement with previous results (*22*), captopril lowered the SBP of the SHR, causing maximum decreases 4–6 h after the administration ($p < 0.05$ by one-way ANOVA). The sequences YRGGLEPINF, RDILNQ, and ESIINF also significantly decreased the SBP of the SHR. In particular, YRGGLEPINF and ESIINF showed a very good antihypertensive activity, reducing by 30 mmHg the SBP in approximately 4–6 h after the administration, although this effect was smaller than that caused by captopril. The other sequence studied, RDILNQ, showed a small blood-pressure-lowering effect that was only statistically significant 2 h after the administration ($p < 0.05$ by one-way ANOVA). The values of SBP always returned to the baseline 24 h after the administration of the different products ($p > 0.05$).

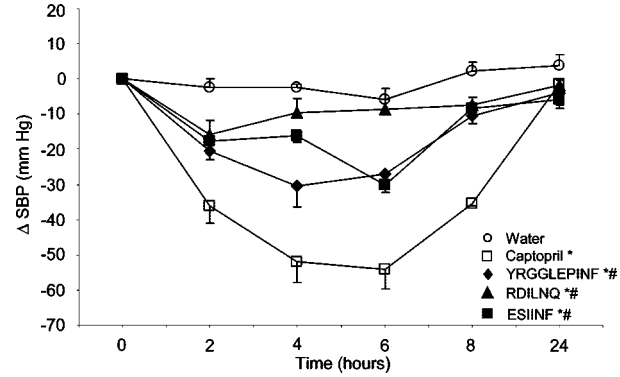


**Figure 2.** Decrease in SBP caused in SHR by the administration of water (○), captopril (50 mg/kg) (□), and the peptides (10 mg/kg): YRGGLEPINF (◆), RDILNQ (▲), and ESIINF (■). The data represent the mean values ± SEM for a minimum of five animals. (*) $p < 0.05$ versus water. (#) $p < 0.05$ versus captopril. $p$ was estimated by a two-way ANOVA.

**Effect of a Simulated Gastrointestinal Digestion on the ACE-Inhibitory Activity, Vascular Effects, and Antihypertensive Properties of the Active Sequences.** The gastrointestinal digestion of the sequences with good antihypertensive properties, YRGGLEPINF and ESIINF, was mimicked by the sequential hydrolysis with pepsin and pancreatic enzymes, and the fragments released by the action of the digestive enzymes were identified by RP-HPLC–MS/MS. The RP-HPLC chro-

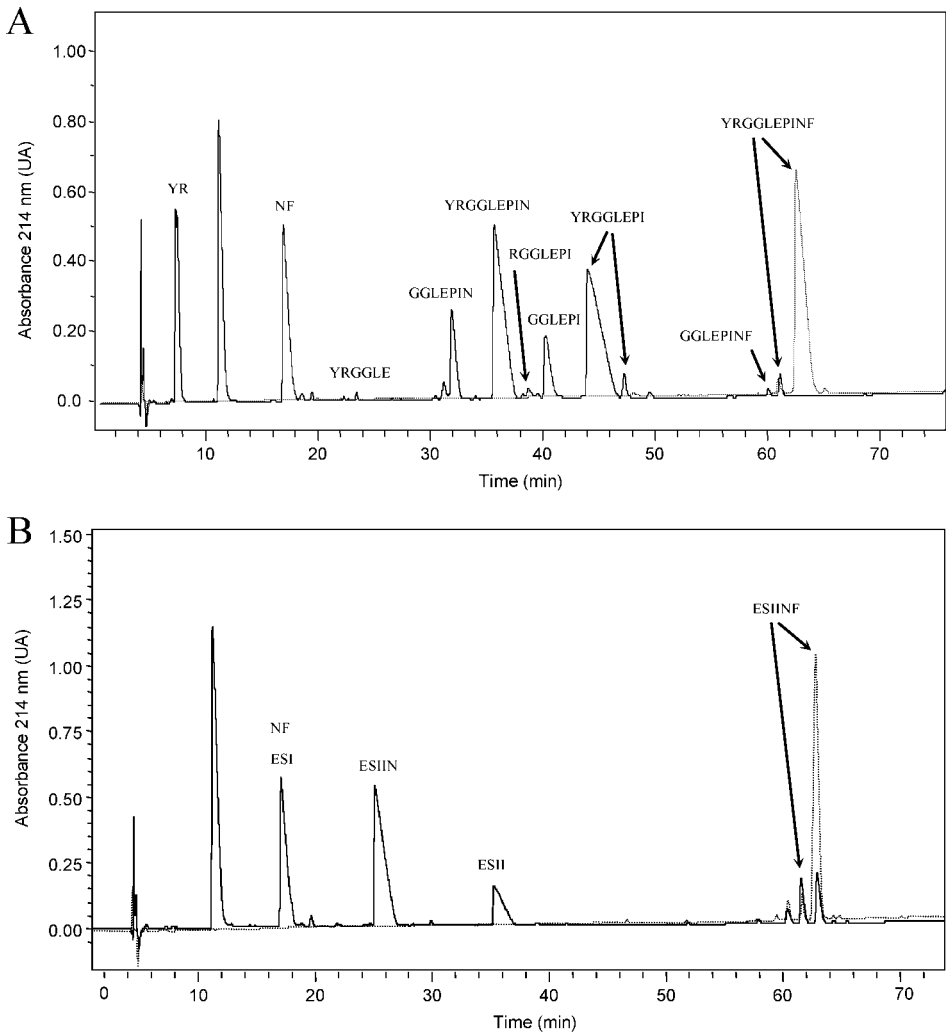


**Figure 3.** RP-HPLC chromatograms of the synthetic peptides YRGGLEPINF (A) and ESIINF (B) submitted to a simulated gastrointestinal digestion. The dotted lines show the RP-HPLC profiles before the digestion.

matograms of the hydrolysates of YRGGLEPINF and ESIINF are shown in parts **A** and **B** of **Figure 3**, respectively. YRGGLEPINF was totally hydrolysed after the incubation with pepsin and the pancreatic extract. The main fragments released were YRGGLEPIN, YRGGLEPI, GGLEPIN, GGLEPI, and the dipeptides YR and NF. A small proportion of the sequences RGGLEPI, GGLEPINF, and YRGGLE were also found (**Figure 3A**). The peptide ESIINF was not completely hydrolysed by the gastrointestinal proteases. The presence of the intact peptide was detected in the final hydrolysate, together with the sequences ESIIN, ESI, and NF and a small amount of the fragment ESII (**Figure 3B**).

The main fragments that resulted from the simulated digestion of YRGGLEPINF and ESIINF, the peptides YRGGLEPI, YR, GGLEPI, NF, and ESI, were chemically synthesized to evaluate their ACE-inhibitory activity *in vitro*, vascular effects, and antihypertensive properties. None of the sequences inhibited ACE *in vitro*, with $IC_{50}$ values above 1000 $\mu$mol/L, except for the dipeptide YR, which presented a moderate ACE-inhibitory activity ($IC_{50}$ = 191 $\mu$mol/L). However, their effects on the vascular function were noticeable. As shown in **Figure 4**, the five peptides studied exhibited vasodilator activity in intact aortic rings precontracted with phenylephrine, causing a relaxation higher than 15%. In particular, the sequences YRGGLEPI and YR produced an important vascular-relaxing effect (approximately 40% of relaxation).

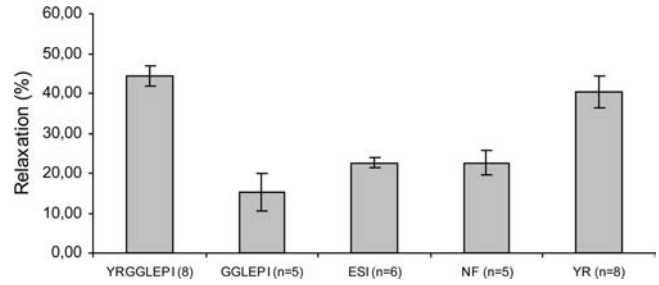


**Figure 4.** Relaxation induced by a single concentration (0.1 mmol/L) of the following peptides: YRGGLEPI, GGLEPI, ESI, NF, and YR in aortic segments from SD. Results (mean ± SEM) are expressed as the relaxation percentage of the contraction previously induced by phenylephrine. The number of animals is shown in the figure.

The vasodilator activity observed for the fragments YRGGLEPI, GGLEPI, ESI, YR, and NF, released upon digestion with gastrointestinal enzymes, suggested that these shorter peptides could be active as antihypertensive components, being responsible for the *in vivo* effect of the original sequences. This hypothesis was checked by performing *in vivo* studies that revealed that the peptides YRGGLEPI, ESI, NF, and YR, significantly reduced the SBP in SHR at doses of 10 mg/kg (**Figure 5**). Conversely, GGLEPI did not show antihypertensive activity.

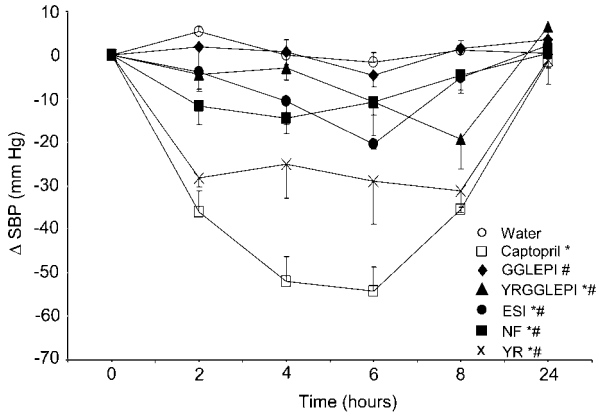


**Figure 5.** Decrease in SBP caused in SHR by the administration of water (○), captopril (50 mg/kg) (□), and the peptides (10 mg/kg): GGLEPI (◆), YRGGLEPI (▲), ESI (●), NF (■), and YR (×). The data represent the mean values ± SEM for a minimum of five animals. (*) $p < 0.05$ versus water. (#) $p < 0.05$ versus captopril. $p$ was estimated by a two-way ANOVA.

## DISCUSSION

In this work, we have identified new antihypertensive sequences derived from egg-white proteins, whose blood-pressure-lowering effect does not rely on an ACE-inhibitory mechanism. The peptides YRGGLEPINF and ESIINF produced an acute antihypertensive effect in SHR upon a single oral administration. However, it seems improbable that the intact sequences are directly responsible for lowering the SBP in these animals, because both were susceptible to proteolytic degradation with gastrointestinal enzymes in a simulated digestion. Our results suggest that the antihypertensive action could be attributed to a vascular-relaxing mechanism that would occur *in vivo* independently of ACE inhibition, because neither these peptides nor their main digestion fragments, except for the dipeptide YR, acted as ACE inhibitors *in vitro*. The vasodilator and antihypertensive activity of the sequences ESI and NF would explain the blood-pressure-lowering effect of ESIINF. With regard to YRGGLEPINF, the low antihypertensive activity of GGLEPI as compared to that of the intact decapeptide points to the dipeptides YR and NF as the main fragments responsible for its activity.

Although structure–activity relationships for vasodilator peptides have not yet been established, our results suggest that certain amino acid residues may contribute to positive vascular effects. Thus, two of the most important vasoactive peptides found in this study, RDILNQ and YRGGLEPINF, possess, respectively, Arg and Tyr in the N-terminal extreme. The importance of the presence of an Arg residue in the amino-terminal position was already highlighted in the case of the vasodilator peptides RADHPFL, RADHPF, and RADHP (*19*, *28*). On the other hand, other vasodilator and antihypertensive sequences derived from ovalbumin, such as YAEERYPIL, YAEER, and YPI, share a Tyr residue in the amino-terminal position (*28*), which is common in antihypertensive food peptides with opioid activity. Thus, Yoshikawa et al. (*14*) isolated two peptides from pepsin–chymotrypsin digests of human casein, casoxin D (YVPFPPF) and casomokinin F (YPFPPF), with endothelium-dependent vasodilator activity in canine mesenteric artery strips. Lebrun et al. (*34*) isolated an octapeptide, YPPVQPFTE, from the trypsin hydrolysate of γ-casein, which displays bradykinin-potentiating activity. Similarly, Sipola et al. (*17*) demonstrated that α-lactorphin (YGLF) and β-lactorphin (YLLF) improved the impaired vascular function in mesenteric arterial rings of adult SHR.

In this respect, the strong vasodilator and antihypertensive properties found in the present work for the dipeptide YR, which may also act as a weak ACE inhibitor, should be highlighted. The dipeptide YR, also named kyotorphin, is an endogenous analgesic neuropeptide in the central nervous system (*35*, *36*). Several studies suggested that kyotorphin may produce various opioid actions via the release of Met-enkephalin in the brain (*37*, *38*). Summy-Long et al. (*39*) reported that the intracerebroventricular injection of kyotorphin caused a transient, dose-dependent increase in blood pressure, reaching a peak after 5 min and returning to basal values either 10 min (100 μg) or 15 min (500 μg) later. However, intravenous injection of the peptide did not cause any significant change in arterial blood pressure during the following 10 min. Various studies show that endogenous opioids can modulate the blood pressure (*40*, *41*). However, the involvement of an endogenous opioid system in cardiovascular regulation is complex because of the existence of numerous opioid peptides and multiple subtypes of opioid receptors both peripherally and centrally. Endogenous opioids and opioid receptors are present in peripheral tissues, including sympathetic ganglia, adrenal medulla, and vascular endothelial cells (*42*, *43*).

In conclusion, this study suggest that certain egg-white-derived peptides significantly reduce the vascular resistance and produce blood-pressure-lowering effects in SHR, independent of ACE inhibition. Although more studies are necessary to clarify the mechanisms responsible for the antihypertensive and vasodilator properties of these sequences, our findings provide new evidence for the potential of egg-white peptides as functional food ingredients with therapeutic benefits in the prevention and treatment of hypertension and other associated disorders.

## ABBREVIATIONS USED

ACE, angiotensin I-converting enzyme; $IC_{50}$, concentration that inhibits 50% of ACE activity; SHR, spontaneously hypertensive rats; HHL, hippuryl-histidil-leucine; KHS, Krebs–Henseleit solution; BCA, bicinchoninic acid; SBP, systolic blood pressure; SD, Sprague–Dawley; RP-HPLC–MS/MS, reversed-phase high-performance liquid chromatography–tandem mass spectrometry; hEW, egg white hydrolysed with pepsin; VALDGGL, Val-Ala-Leu-Asp-Gly-Gly-Leu; SALAM, Ser-Ala-Leu-Ala-Met; RDILNQ, Arg-Asp-Ile-Leu-Asn-Gln; FSL, Phe-Ser-Leu; YRGGLEPINF, Tyr-Arg-Gly-Gly-Leu-Glu-Pro-Ile-Asn-Phe; ELIN, Glu-Leu-Ile-Asn; YQIGL, Tyr-Gln-Ile-Gly-Leu; VLLPDEVSGL, Val-Leu-Leu-Pro-Asp-Glu-Val-Ser-Gly-Leu; ESIINF, Glu-Ser-Ile-Ile-Asn-Phe; DGSRQPV, Asp-Gly-Ser-Arg-Gln-Pro-Val; YRGGLEPI, Tyr-Arg-Gly-Gly-Leu-Glu-Pro-Ile; GGLEPI, Gly-Gly-Leu-Glu-Pro-Ile; ESI, Glu-Ser-Ile; NF, Asn-Phe; RADHP, Arg-Ala-Asp-His-Phe; RADHPF, Arg-Ala-Asp-His-Pro-Phe; RADHPFL, Arg-Ala-Asp-His-Pro-Phe-Leu; YAEER, Tyr-Ala-Glu-Glu-Arg; YAEERYPIL, Tyr-Ala-Glu-Glu-Arg-Tyr-Pro-Ile-Leu; YPI, Tyr-Pro-Ile; YVPFPPF, Tyr-Val-Pro-Phe-Pro-Pro-Phe; YVFPPF, Tyr-Val-Phe-Pro-Pro-Phe; YPPVQPFTE, Tyr-Pro-Pro-Val-Gln-Pro-Phe-Thr-Glu; YGLF, Tyr-Gly-Leu-Phe; YLLF, Tyr-Leu-Leu-Phe; YR, Tyr-Ala.

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