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ORIGINAL ARTICLE

The lectin isolated from *Lonchocarpus araripensis* seed elicits endothelium-dependent vasorelaxation

A lectina isolada de sementes de *Lonchocarpus araripensis* promove efeito vasorelaxante dependente de endotélio

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Abstract

Background: The vasorelaxant effect of lectins from leguminous plants (Diocleinae subtribe) is well described. However, this effect has been little explored for lectins isolated from Dalbergieae tribe, except for that of *Vatairea guianensis*, that induces vasorelaxation involving nitric oxide and the lectin domain. **Objective**: To evaluate the vasorelaxant effect of a lectin isolated from *Lonchocarpus araripensis* (LAL), Dalbergieae tribe, and the involvement of the lectin domain and endothelium derived relaxing factors. **Methods**: Aortic rings of Wistar rats (250 - 300 g) were mounted in organ bath and mantained in physiological conditions (CEUA No. 10130208-8/40). LAL (0.1–100 μg/ml) was added to phenylephrine (0.1 μM)-contracted tissues with either endothelium intact or denuded. In order to investigate the mechanisms of LAL relaxation, inhibitors of NOS (L-NAME: 100 μM), cyclooxygenase (indomethacin: 10 μM), or potassium channels (TEA: 5 mM) were added to endothelized tissues 30 min before contraction. The involvement of lectin domain was assessed by previous incubation of LAL (30 μg/ml) with GlcNAc (0.1 M). **Results**: LAL (0.1-100 μg/ml) induced relaxation only in endothelized aorta, being maximal at 100 μg/ml (62.57 ± 7.8%). The relaxant effect induced by LAL at 30 μg/ml (52.49 ± 10.32%) was abolished by previous incubation with GlcNAc. LAL relaxant effect (IC50 9.75 ± 7.1) was partially reversed by indomethacin (IC50 LAL + indomethacin: 30.47 ± 10.93) and was abolished by L-NAME or TEA. **Conclusion**: LAL exhibits vasorelaxant activity in contracted endothelized aorta of rats, involving the lectin domain, muscarinic receptor of acetylcholine and endothelial derived relaxing factors.

Key words: Lonchocarpus araripensis. Lectin. Vasorelaxant effect. Endothelium-derived relaxing factors. Lectin domain.

Resumo

Introdução: O efeito vasorrelaxante de lectinas de plantas leguminosas (Subtribo Diocleinae) já é bem descrito, embora pouco explorado para lectinas isoladas da tribo Dalbergieae, com exceção da lectina de *Vatairea guianensis*, que induz relaxamento com envolvimento de óxido nítrico e do domínio lectínico. **Objetivo**: Avaliar o efeito vasorrelaxante da lectina isolada de *Lonchocarpus araripensis* (LAL), tribo Dalbergieae, e o envolvimento do domínio lectínico e de fatores relaxantes derivados do endotélio (EDRF). **Métodos:** Anéis de aorta de ratos Wistar (250-300 g) foram montados em banho de órgãos em condições fisiológicas (Tyrode, 37 ° C, 95% de O2 e 5% de CO2, pH = 7,4) (CEUA No. 10130208-8/40). LAL (0,1-100 μg/ml) foi adicionada a tecidos pré-contraídos com fenilefrina (0,1 μM) com ou sem endotélio. Para investigar os mecanismos de relaxamento, foram adicionados inibidores de NOS (L-NAME: 100 μM), guanilato ciclase (ODQ: 10 μM), receptor muscarínico (atropina: 1 μM), ciclooxigenase (indometacina: 10 μM) ou canais de potássio (TEA: 5 mM) aos tecidos endotelizados 30 minutos antes da contração. O envolvimento do domínio lectínico foi avaliado por incubação prévia da LAL (30 μg/ml) com GlcNAc (0,1 M). **Resultados**: LAL (0,1-100 μg/ml) relaxou apenas anéis de aorta endotelizadas, com efeito máximo na dose de 100 μg/ml (62,57 ± 7,8%). O efeito relaxante da LAL a 30 μg/ml (52,49 ± 10,32%) foi abolido por incubação prévia com GlcNAc, atropina ou ODQ. O relaxamento da LAL (IC50 9,75 ± 7,1) a 10, 30 e 100 μg/ml foi parcialmente revertido por indometacina (IC50 LAL + indometacina: 30,47 ± 10,93) e abolido por L-NAME e TEA. **Conclusão:** A LAL exibe atividade vasorrelaxante em aorta endotelizada de ratos, no estado contraído, envolvendo o domínio lectínico, receptor muscarínico e fatores relaxantes derivados do endotélio.

Palavras-chave s: Lonchocarpus araripensis. Lectina. Efeito vasorrelaxante. Fatores relaxantes derivados do endotélio. Domínio Lectínico.

INTRODUCTION

Lectins are proteins possessing at least one non-catalytic lectin domain by which they reversibly bind to specific mono or oligosaccharides[1]. Plant lectins isolated from the Leguminosae family have been considered important tools in biological models, since they present structural similarities but differ in their activities[2].

Leguminous lectins belonging to Diocleinae subtribe are well described regarding their in vitro vasodilator effect, which involves the lectin domain and endothelial-derived relaxant factors, specially nitric oxide (NO)[3-6]. However, for lectins isolated from the tribe Dalbergieae, the vasodilator effect has been little explored, except for that isolated from *Vaitarea*

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guianensis, which induces relaxation via NO and the lectin domain[7]. Particularly, only few investigations report the effect of lectins of the genus Lonchocarpus in nociception and inflammation models, but there is no data about its i*n vitro* vasodilator effects[8-11]. In this line, investigations of new vasodilator substances could ameliorate several symptoms of pathological conditions involving endothelial disfunction, such as diabetes and hypertension.

The aim of the present study was to investigate the vasorelaxant effect of *Lonchocarpus araripensis* lectin (LAL) and the involvement of the lectin domain and endothelium-derived relaxing factors (EDRF).

MATERIALS AND METHODS

Materials

N-acetylglucosamine (GlcNAc), indomethacin, Nw- nitro-L-arginine-methyl ester (L-NAME), 1H-[1,2,4]Oxadiazolo-[4,3-a] quinoxalin-1-one (ODQ), phenylephrine (PE), acetylcholine (ACh), tetraethylammonium (TEA) and atropine were purchased from Sigma Chemical (St. Louis, MO, USA). All drugs and the lectin were solubilized in 0.15 M sterile NaCl (saline), except for indomethacin, which was dissolved in dimethyl sulfoxide up to 10% of total volume and then in saline.

Animals

Male Wistar rats (250-300 g) were maintained with a 12/12 h light/dark cycle at 25 ºC with free access to food and water. The experimental protocols were approved by the Institutional Animal Care and Use Committee of the State University of Ceará (CEUA/UECE No. 10130208-8/40).

Lectin

LAL was isolated from seeds of *Lonchocarpus araripensis* (family Leguminosae, subfamily Faboideae, tribe Dalbergiae) by affinity chromatography followed by ion exchange chromatography (DEAE-Sephacel)[11].

Tissue preparation

Thoracic rat aorta was removed, cleaned and sectioned in ring segments (3-5 mm). Aortic rings were mounted for tension recording (2 g) in organ baths filled with modified Tyrode solution (in mM: 136 NaCl, 5 KCl, 0.98 $MgCl_2$, 2 $CaCl_2$, 0.36 NaH2PO4, 11.9 NaHCO3, and 5.5 glucose) at 37°C, 95% O2 and 5% CO2, pH=7.4. Aorta was challenged with KCl (60 mM) after at least 45 min of equilibrium to assure tissue viability. The contractile response was measured using a force transducer, coupled to a pre-amplifier and computerized data acquisition system (Chart - PanLab). Remotion of endothelium was assessed by mechanical rubbing of the aorta intimal surface. The intact endothelium was considered for relaxant responses to ACh greater than 75% of the Phe-induced tone[12].

Investigation of LAL relaxant effect in isolated aorta

Cumulative concentration of LAL (0.1–100 µg/ml) were performed at the contraction plateau induced by Phe (0.1 µM) or at aorta basal tonus in either endothelium intact or denuded. Control group received the same volume of Tyrode. The participation of lectin domain was assessed by the previous incubation of LAL (30 µg/ml) in solution with GlcNAc (0.1 M) for 60 min at 37°C, to allow lectin-sugar interactions, before performing experimental protocols. LAL and GlcNAc were also incubated in separated solutions at the same conditions as controls. For the involvement of EDRF in the lectin relaxation, inhibitors of NOS (L-NAME; 100 µM), cyclooxygenase (indomethacin; 10 µM), guanylyl cyclase (ODQ; 10 µM), muscarinic receptor (atropine; 1 µM), or potassium channels (TEA; 5 mM) were added to the endothelized tissues 30 min before Phe.

Statistical analysis

Data was presented as Mean ± S.E.M (n = 4-6) and analyzed by Student's t test or ANOVA, followed by Bonferroni's post-test, being considered significant p values less than 0.05.

RESULTS

LAL induces relaxation in endothelized aorta

Phenylephrine induced tonic contractions in aorta with amplitude of 0.87 ± 0.04 g (n=13) in the absence and 0.54 ± 0.03 g (n=11) in the presence of endothelium. Cumulative addition of LAL to precontracted tissues did not affect endothelium-denuded preparations (Figure 1A, C). The aorta basal tonus was also not altered by LAL (data not shown). However, in aorta with intact endothelium, LAL induced significant relaxation that was initiated at 0.1 µg/ml and attained maximal effect at 100 µg/ml by 62.57 ± 7.8% (IC50= 9.75 ± 7.1) (Figure 1B, C). LAL did not alter the tissue responsiveness, since, at the end of each experiment, KCl-contractile response was similar to the initial tone (Figure 1A, B).

The relaxant effect of LAL was inhibited by GlcNAc and EDRF blockers

The relaxant effect induced by LAL at 30 µg/ml (52.49 ± 10.32 %) was abolished by previous incubation with GlcNAc, atropine or ODQ (Figure 2A). LAL relaxant effect (IC50 9.75 ± 7.1) at the doses of 10, 30 and 100 µg/ml was partially reversed by indomethacin (IC50 LAL + indomethacin: 30.47 ± 10.93) and abolished by L-NAME and TEA (Figure 2B).

Figure 1. LAL induces relaxation in endothelized aorta precontracted with phenylephrine. Typical traces of cumulative addition of LAL (0.1–100 µg/ml) to precontracted tissues in (A) denuded or (B) endothelized aorta; (C) Comparison of LAL response in denuded (E-) or endothelized (E+) aorta. Mean ± S.E.M. (n=5-7); *p<0.05 vs. 100% Phe-induced contraction. Phenylephrine (Phe: 0.1µM); acetylcholine (ACh: 1 µM), potassium chloride (KCl: 60 mM); washing with Tyrode (W).

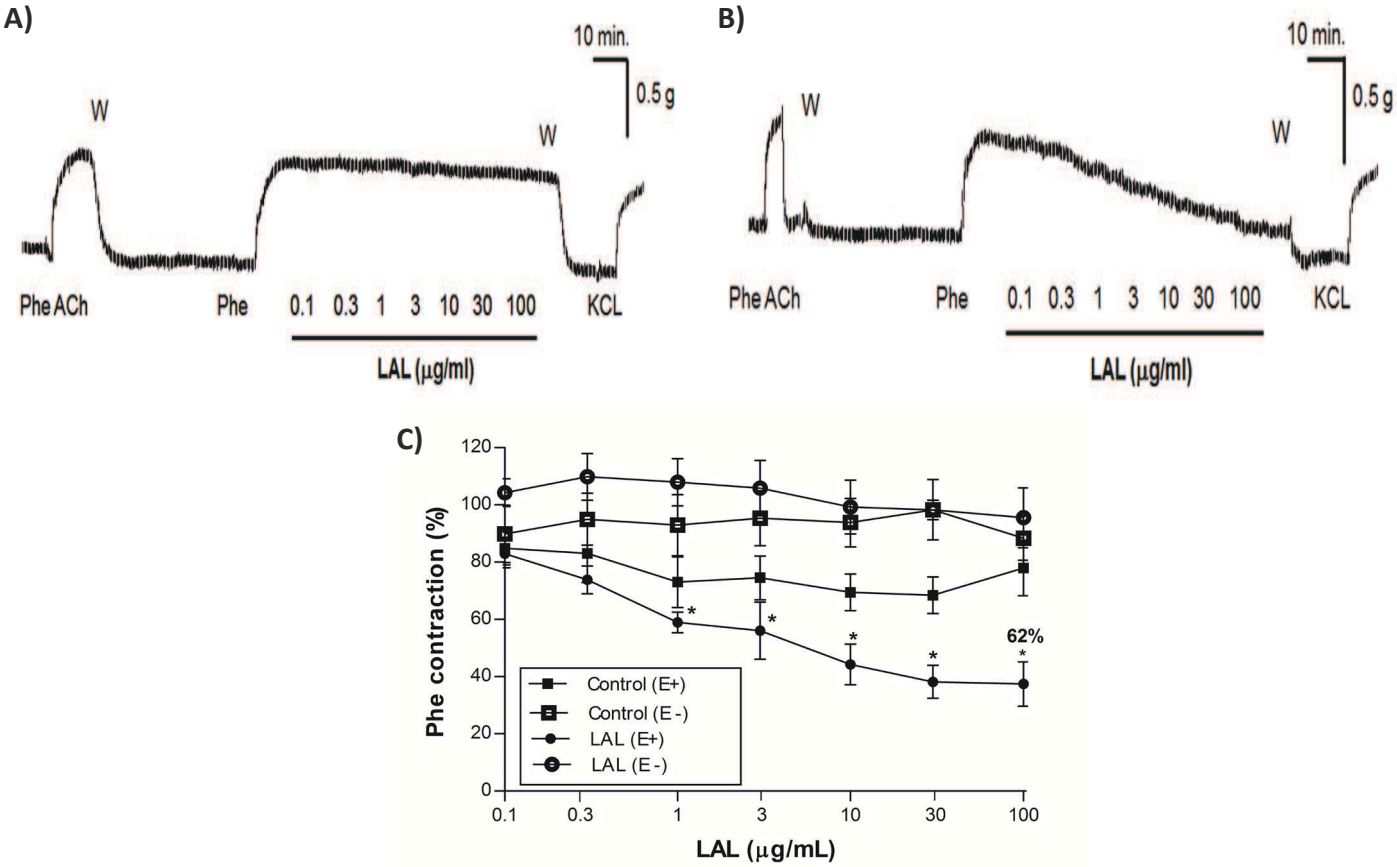
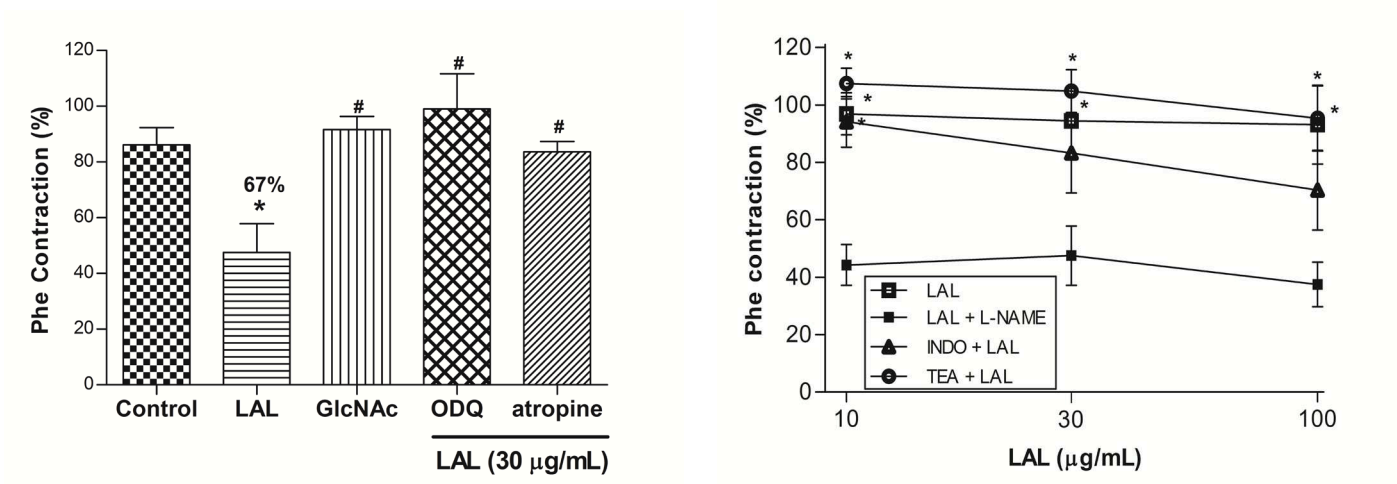


Figure 2. Role of lectin domain and endothelium derived relaxant factors in the LAL vasorelaxant effect. A) LAL (30 µg/mL) in presence of GlcNAc, 1H-[1,2,4]Oxadiazolo-[4,3-a]quinoxalin-1-one (ODQ: 10 µM) and atropine (1 µM); B) LAL (10-100 µg/mL) in presence of INDO, TEA or L-NAME. Mean ± S.E.M. (n=5-7); *p<0.05 vs. control (100% Phe-induced contraction); #p<0.05 vs. LAL. N-acetyl-glucosamine (GlcNAc: 0.1 M); Phenylephrine (Phe: 0.1 µM); acethylcholine (ACh: 1 µM); potassium chloride (KCl: 60 mM); indomethacin (INDO: 10 µM); tetraethylammonium (TEA: 500 µM); N-nitro-L-arginine methyl ester (L-NAME: 100 µM).



DISCUSSION

The present study demonstrated that the lectin of *Lonchocarpus araripensis* (tribe Dalbergieae) induces relaxation in pre-contracted aorta via lectin domain, an effect strictly dependent on the intact endothelium. Other leguminous lectins had induced relaxation in rat endothelized aorta with the involvement of carbohydrate binding sites[4,5,13,14], including the lectin of *Vatairea guianensis* also belonging to the tribe Dalbergieae[7].

Endothelium-dependent vasodilation is mediated by factors such as nitric oxide (NO), prostacyclin and endothelium-derived hyperpolarizing factor (EDHF)[15]. Many studies have shown that leguminous lectins, similar to LAL, present as the main mechanism the induction of relaxation of endothelized aorta the NO pathway[4,5]. It is well known that NO, the principal endothelial relaxant factor, is produced via eNOS activation in response to agonists such as acetylcholine, bradykinin and substance P, or via mechanical stimulation, such as shear stress[16]. After diffusion into adjacent smooth muscle cells, NO activates the soluble guanylate cyclase, leading to the increase of intracellular cGMP and relaxation[17].

In this study, the demonstration of the blockade of LAL-induced relaxation with L-NAME, and also by GlcNAc suggests the lectin interaction with carbohydrate sites present in endothelial cells, leading to NO release. In fact, previous evidence had suggested the binding of lectins to vascular endothelial cells via carbohydrate residues[18,19].

Once the participation of NOS in the LAL effect hab been demonstrated, aortas were incubated with atropine, antagonist of muscarinic receptors of acetylcholine, and ODQ, guanylyl cyclase blocker. Atropine abolished the relaxing effect of LAL on endothelized aortas, as previously observed in other leguminous lectins, such as Pisum arvense[6,20]. This LAL effect was also abolished by tissue incubation with ODQ, showing the participation of the enzyme guanylyl cyclase in the relaxing effect of LAL. Previous evidence suggests that lectins can bind to vascular endothelial cells[19], which may result in NO release and activation of guanylate cyclase in vascular smooth muscle, reduction in calcium concentration and the consequent vascular relaxation[21, 22].

In addition, indomethacin partially reduced LAL relaxant effect, indicating the participation of prostacyclin, the major product of ciclooxygenase pathway in endothelial cells[23], that mediates relaxation via activation of adenylyl cyclase increasing cAMP in vascular smooth muscles[24]. The Moreover, LAL-induced relaxation was also blocked by tetraethylammonium, suggesting the participation of EDHF, which promotes dilatation of vascular smooth muscle via K+ channels activation and membrane hyperpolarization[25]. The participation of prostacyclin and EDHF in the relaxant effect of leguminous lectins had already been described[4].

Studies have shown the association of NO, prostacyclin and EDHF in vasorelaxation. Prostacyclin facilitates NO release from endothelial cells[23], which activates cGMP synthesis, inhibits phosphodiesterase and inactivates cAMP[26, 27], potentiating prostacyclin effects in the smooth muscle. Other studies had described the direct activation of Ca2+ dependent K+ channels (Kca) via NO excluding cGMP[28]. This connection between NO and EDHF could explain the abolishment of LAL relaxant effect by L-NAME or TEA.

In conclusion, LAL exhibits vasorelaxant activity in phenylephrine-contracted endothelized aorta of rats, involving the lectin domain, muscarinic receptor of acetylcholine and endothelial derived relaxing factors.

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