Acta Veterinaria (Beograd), Vol. 49. No. 4, 221–230, 1999.

UDK 619:615.225

THE EFFECT OF THE NO-SYNTHASE INHIBITORS ON THE CONTRACTION OF THE ISOLATED BOVINE ABDOMINAL AORTA INDUCED BY NORADRENALINE IN THE PRESENCE OF LPS-ENDOTOXINS

MIRJANA MILOVANOVIC and MILANKA JEZDIMIROVIC

Faculty of Veterinary Medicine, Bul. JNA 18, Belgrade, Yugoslavia, Department of Morphology and Physiology

(Received, 10 May 1999.)

Lipopolysaccharides (LPS) are endotoxins present in gram-negative bacteria, that cause of insufficiency in the cardiovascular system and damage to the internal organs. It has been shown that LPS and cytokines (TNF, IL-1 and INF-γ) act upon the endothelium of blood vessels, activiting the enzymes, inducible NO-synthase and cyclo-oxygenase (COX-2). At the same time, LPS induces marked synthesis and release of nitric oxide (NO) and prostacyclin (PGI_2). These endothelial mediators (NO and PGI_2) relax the vascular smooth muscle, thus bringing about proncunced vasodilatation and hypotension. They also cause a hyporeactive effect of the blood vessels to the vasoconstrictive drug. Having in mind theimportance of NO in the pathogenesis of septic shock, we undertook to examine the effect of the NO-synthase inhibitors, N^G-nitro-L- arginine methyl ester (L-NAME) and dexamethasone on the contraction of isolated bovine abdominal aorta induced by noradrenaline in the presence of LPS.

After an incubation of 4 hours, the lipopolysaccharide from E. coli 055:B5, depressed the contractile effect of noradrenaline on isolated bovine abdominal aorta. This LPS depressing effect was antagonised by the NO-synthase inhibitor (L-NAME). This L-NAME specific effect was confirmed by the administration of L-arginine (as a NO donor), that antogonised the L-NAME effect, i. e. it reversed the depressed contractile effect of noradrenaline in the presence of LPS. Dexamethasone, after an incubation period of 20 minutes, did not affect the decreased contractile effect of noradrenaline induced by LPS. However, after incubation for 60 minutes, this glucocorticosteroid eliminated the LPS depressing effect on the isolated aorta contractions, produced by noradrenaline. The obtained results show that the L-arginine NO system has an important role in the development of lowered reactivity of the isolated bovine abdominal aorta to noradrenaline in thepresence of LPS. Therefore, an early application of the specific inhibitors NO-synthase and dexamethasone could prove very useful in the prevention of progressive vasodialatation during septic shock.

Key words: Lipopolysaccharide, NO-synthase, L-NAME, dexamethassone, noradrenaline, bovine abdominal aorta.

INTRODUCTION

Lipopolysaccharide (LPS) derived from gram-negative bacteria is an endotoxin that produces progressive vasodilatation, hyporeactivity of blood vessels to vasoconstrictive drugs, as well as an increases permeability of the vascular system, in an organism, i. e. septic shock (Rees at al., 1996). An enzyme, the inducible NO-synthase (INOS), takes an important place in the pathogenesis of this cardiovascular disorder. It is synthesized and adivated in the vascular endothelial and smooth muscle celle and cardiac myocytes under the influence of LPS and cytokines, such as tumor necrotic factor (TNF), interleukin-1 (L-I) and interferon-y (NF-γ) (Thiemermann, 1995). INOS adivation synhesizes and relaases an extra amount of nitric oxide that produces relaxation of the smooth vascular muscles, i. e. pronounced vasodilatation and hypotension (Parratt, 1995; Kumar et al., 1997). However, under physiological conditions, the vascular endothelium with the help of the conscitutive NO-synthase (cNOS) produces a small amount of NO, which, as a vasodilative mediator, participates in the maintenance of the physiological tonus of blood vesseels (Moncada et al., 1991; Forstermann and Kleinert, 1995).

The specific inhibitor of iNOS, N^G-nitro-L-arginine methyl ester (L-NAME) is an analogue of L-arginine, an aminoacid that acts the within the body as a NO donor. This inhibitor blocks the activity of the constitutive and inducible NOS, i. e. the synthesis and release of NO from the vascular endothelium (Adams, 1995; Bryant et al., 1995).

Dexamethasone is a synthetic gluccorticosteroid that has been shown to inhibit iNOS activation, without any effect on the already activated enzyme. Within the vascular smooth muscle cells it increases the production of lipocortin-1 (LC-1), a protein with a role of "second messenged" in its antiinflammatory effect. Within a cell LC1 binds to iNOS and blocks the activation of this enzyme (Cannon et al., 1998; Bryant et al., 1998).

The goal of our experiments, was to examine whether and for how long LPS from E. coli depresses the contractile effect of noradrenaline on isolated bovine abdominal aorta. Al the same time we undertook to determine whether the inhibitors NO-synthase, L-NAME and dexamethasone could eliminate the depressive effect of LPS on the contraction of isolated blood vessels.

MATERIAL AND METHODS

The experiments were performed on the isolated abdominal aorta of male Simmenthal cattle, aged 12 to 14 months and of body weight about 500 kg. A part of the abdominal aorta was always dissected from the same anatomical region, i. a. between the last thoracic and second lumbar vertebra. The isolated blood vessels were cut into rings, 3-5 mm wide, and immersed in organ baths, containing 25 ml of nutritive medium(Tyrode solution) of the following composition" NaCl 137, KCl 2,6, $CaCl_2$ 1.8, $MgCl_2$ 0.1, NaH_2 PO_4 0.42, $NaHCO_3$ 11.9 and glucose 11.1 (in mM). The medium was aerated with a mixture of oxygen (95%) and carbon dioxide (5%), at a constant temperature of 37^0C and pH 7.2.

The isometric contraction of the isolated aorta was recorded by an isometric transducer and preamlifier (Ugo Basile 7080) on the "Gemini" 2-channel recorder (Ugo Basile 7070), with an initial pereloading of the preparation of 2.5g.

For each experiment two segments of the same blood vessel were used, one of them being the control; whereas in the organ bath of the second segment the endotoxin, LPS, from E.coli was added at the concentration of 1μg/ml. The segments were first incubated in the organ bath for 4 hours, and consequently treated with noradrenaline (from 0.1×10^{-7}M to 0.35×10^{-8}M). Every registration of the noradrenaline effect in the presence of LPS (1μg/ml), L-NAME (10^{-6}M), L-arginine (10^{-3}M) and dexamethasone (10^{-6}M) was repeated six times, i. e. 6 isolated segments of blood vessels taken from 6 animals. The following substances were used: LPS from E .coli 055:B5 (Difco Laboratories), N^G nitro-L-arginine methyl ester (L-NAME) (Sigma), L- arginine (Sigma), dexa-methasone (Deksazon®) (ICN Galenika) and noradrenaline hydrochloride (Serva).

The obtained results are expressed as the mean + s.e. m. in percentages (%) of the greatest contractile effect observed (100%). Statistical evaluation was done by the paired and unpaired Student's test for the dependent measurements and the Test of Parallelism for the probablity levels 0.05 and 0.01.

RESULTS

Noradrenaline (0.1×10^{-7}M to 0.19×10^{-6}M) produced a concentration dependent contraction of the isolated bovine abdominal aorta, after incubation in a isolated organ bath for 4 hours. (Figure 1.) The greatest response was assigned a value of 100%.

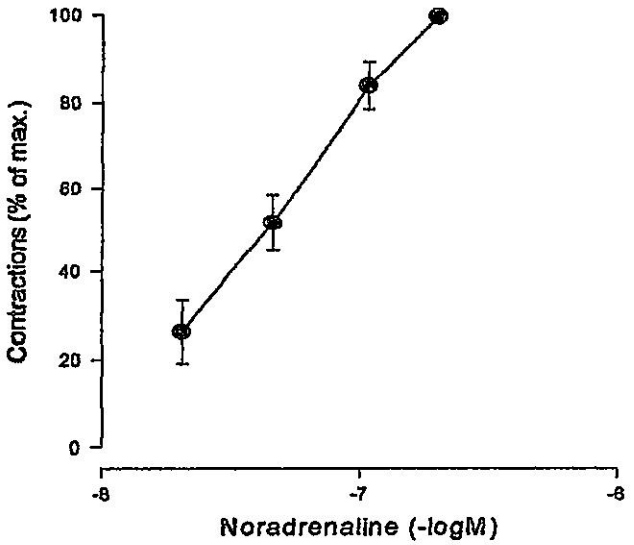

Figure 1. The dose-response curve indicating the contactile effect of increasing concentrations of naradrenalline on the isolated bovine abdominal aorta, incubated for 4 hours in Tyrade solution. The isometric contraction increase of the maximal achievable contractile effect is shown on the ordinate. Data are expressed as mean + s.e.m. of (n=6) observations.

Lipopolysaccharide from *E. coli* (1μg/ml), produced a significant decrease ($P<0.01$) in the contractile effect of noradrenaline on the isolated bovine abdominal aorta, compared to the control. The cumulative concentration dependent curve for noradrenaline in the presence of LPS was shifted to the right in relation to the control concentration dependent curve (Figure 2). Thus, LPS significantly reduced the noradrenaline contractile effect, so that noradrenaline at the concentration of $0.19x10^{-6}$M produced a contraction of only 51.65% of the control value (Fig.3). Twice as much noradrenaline ($0.35x\ 10^{-6}$M), resulted in a slight increase in the contraction of the isolated bovine abdominal aorta to 63.42%.

In the presence of the inhibitor of NO-synthase L-NAME (10^{-3}M - incubation period of 30 min.) and LPS, the contractile effect of noradrenaline was significantly more pronounced ($P<0.05$) than its contractile effect in the presence of endotoxin alone. Thus, noradrenaline ($0.35x10^{-6}$M), in the presence of both L-NAME and LPS, produced a 100% contractile effect (Figure 2 and 3). The cumulative concentration-response curve for noradrenaline in the presence of LPS and L-NAME was shifted to the left in comparison to the concentration-response curve for noradrenaline in the presence of LPS alone.

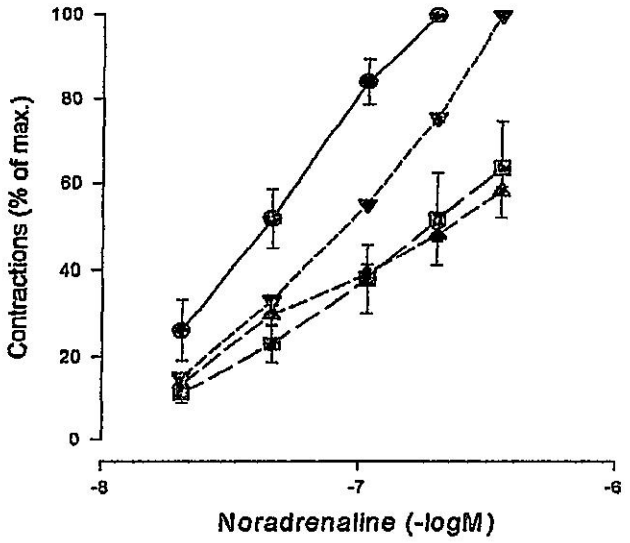

Figure 2. The dose-respores curves indicating the effects of L-NAME and L-arginine on the responsiveness to increasing concentratioins of noradrenaline of isolated bovine abdainal aorta, to the presence of LPS. The line marked with circles (●), which is the control dose-response line in all experiments, shows the dose-response relationship for noradrenaline in preparations incubated only in Tyroide solution for 4h. The line marked with squares (|), shows the dose-response relationship for noradrenaline in preparations incubated in the presence of LPS (1μg/ml) for 4h. The line marked with triangles (Δ), shows the dose-response relationship for noradrenaline in preparations incubated in the presence of both LPS and L-NAME (10^{-6}M) for 4h. The line marked with invarted triangles (V) is the dose-response curve showing the effect of increassing concentrations of noradrenaline in the presence of LPS, L-NAME and L-arginine (10^{-6}M) for 4h.

If the isolated bovine abdominal aorta was incubated in the presence of L-arginine (10^{-3}M) - incubation period of 30 mmin.), L-NAME and LPS, the contractile effect of noradrenaline was significantly weaker ($P<0.01$) than in the presence of L-NAME and LPS, L-NAME and L-arginine, was shifted to the right, compared to that for noradrenaline in the presence of LPS and L-NAME alone. Thus, the contractile effect of noradrenaline ($0.35x10^{-6}$M), in the presence of L-arginine, L-NAME and LPS amounted only to 60.11% of that under the same conditions but without L-arginine.

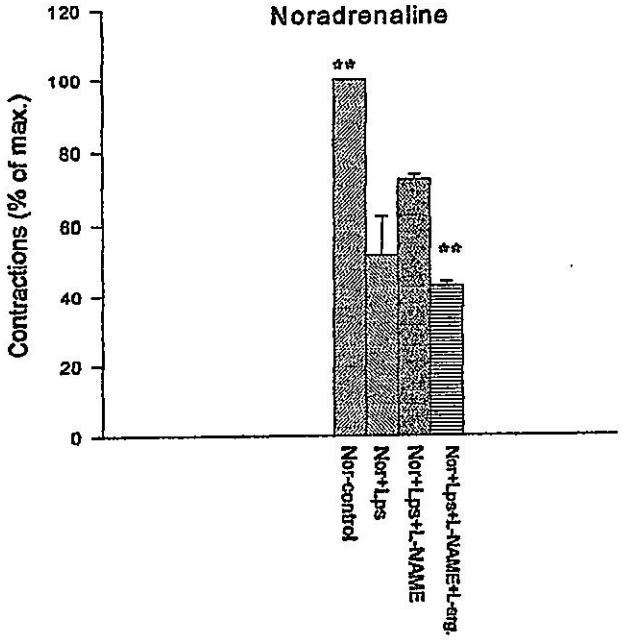

Figure 3. Effects of L-NAME and L-arginine on the responsiveness to increasing concentrations of noradrenaline of isolated bovine abdominal aorta, to the presence of LPS. Data are expressed as mean + s.e.m. of (n=6) obseervations; **P<0.01 versus Nor-control.

Dexamethasone (10^{-6}M - incubation periods of 20 min, and 60 min.) did not directly affect the contractile effect of noradrenaline on bovine abdominal aorta. Namely, the cumulative concentration- response curves for noradrenaline alone and in the presence of dexamethasone (incubation periods of 20 and 60 min.) were nearly identical (Figure 4.).

After an incubation period of 20 min. dexamethasone in the presence of LPS did not change significantly the noradrenaline contractile effect, compared that in the presence of LPS alone. Namely, the cumulative concentration-response curves for noradrenaline in the presence of LPS and dexamethasone (incubation period of 20 min.) and noradrenaline in the presence of only LPS coincided (Figure 5). The contractile effects of noradrenaline ($0.35x10^{-6}$M) in

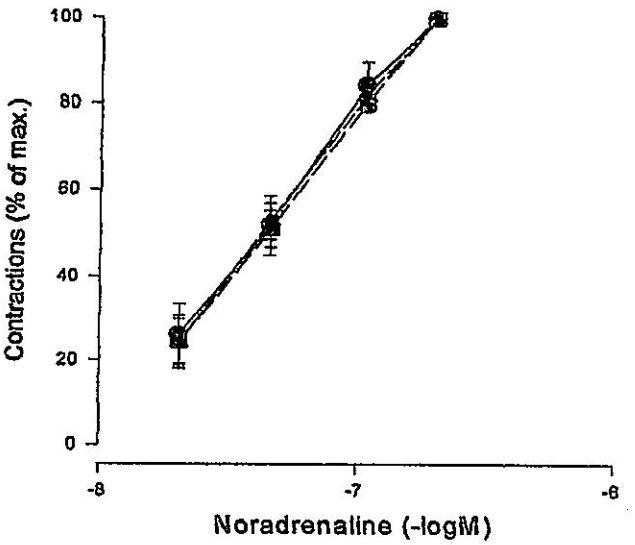

Figure 4. The dose-response curves indicating the effect of dexamethasanee on the responsiveness to increasing concentrations of noradrenaline of isolated bovine abdominal aorta. The line marked with cincles (•) is the control dose- response line (see fig. 1 and 2.). The line marked with triangles (Δ), shows the dose-response relationship for noradrenaline in preparations incubated in the presence of dexamethasone (10^{-6}M - incubated for the last 20 min.). The line marked with invected triangles (▽), is the dose-response curve, showing the effect of increassing concentrations of noradrenaline in the presence of dexamethasone (10^{-6}M - incubated for the last 60 min). It is noticeable that these dose-response lines overlap.

the presence of LPS and dexamethasone (incubation period of 20 min) amounted to 58.18%; whereas the contractile effect of noradrenaline in the presence of only LPS was insignificantly stronger and amounted to 63.42%. However, after incubation with dexamethasone, for 60 min. and LPS, the noradrenaline contractile effect was significantly stronger ($P<0.05$). The cumulative concentration-response curve for noradrenaline in the presence of LPS and dexamethasone (incugation period of 60 min.) was shifted to the left compared to that in the presence of LPS alone. Namely, noradrenaline (0.35 x 10^{-6}M) in the presence of dexamethasone (incubation period of 60 min.) and LPS, produced a 100% contractile effect (Figure 6.).

DISCUSSION

It is well krown that noradrenaline is a mediator of the adrenergic nervous system, that may produce either contraction or relaxation of smooth muscles. Its contractle effect on vascular smooth muscle is achieved via alpha-adrenergic receptors. Relaxation of smooth muscle is the result of the activation of beta$_2$-adrenergic receptors, to which noradrenaline shows much weaker affinity (Hoffman and Lefkowitz, 1995).

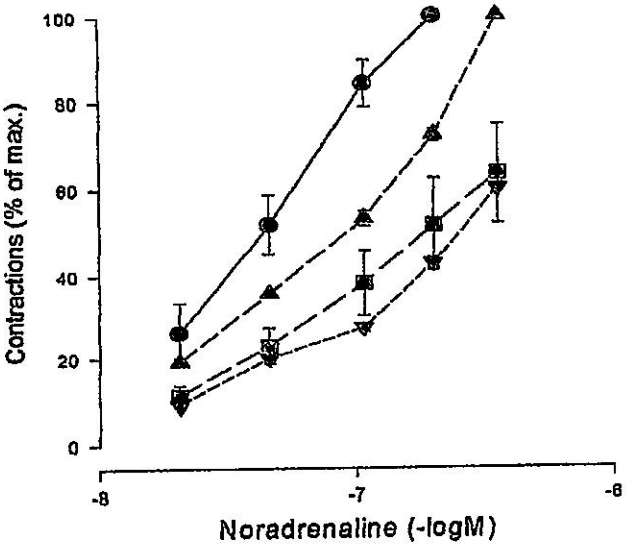

Figure 5. The dose-response curves indicating the effect of dexamethasane on the responsiveress to increasing concentrations of noradrenaline of isolated bovine abdominal aorta to the presence of LPS. The line marked with circles (●) is the control dose-response line. The line marked with aquares (□), shows the dose-response relationship for noradrenaline in preparations incubated in the presence of LPS (1 μg/ml) for 4h. The lin marked with triangles (Δ), shows the dose-response relationship for noradrenaline in preparations incubated for 4h, in the presence of both LPS and dexamethasone (10^{-6}M - incubated for the last 20 min). The line marked with inverted triangles (▽), is the dose response curve, showing the sifect of increassing concentrations of noradrenaline for 4h, in the presence of both LPS and dexamethasone (10^{-6}M - incubated for the last 60 min).

During this experiment noradrenaline alone, at the concentration of 0.19 x 10^{-6}M, produced the greatest contractile effect on isolated bovine abdominal aorta.

In the presence of LPS from E. coli the contractile effect of noradrenaline was markedly reduced, in accordance with earlier findings of other authors (Wu et al. 1994; Villamor et al., 1995; Isao et al., 1995). In the endothelium and smooth muscles of isolated blood vessels, LPD activates the inducible NO-synthase (iNOS), that affects L-arginine, thus releasing nitric oxide (NO) (Moncada et al., 1991; Szabo et al., 1993). As a highly reactive free radical, NO passes into the cytosol of smooth muscle vascular cells and activates the enzyme, soluble guanylyl cyclase (sGC). This activation in smooth muscle vascular cells increasses the accumulation of cGMP which produces vasodilatation of smooh muscle blood vessels (Wu et al., 1994; Shulz and Triggle, 1994). Namely, under the influence of the endotoxin LPS an excessive synthesis of NO occurs, resulting in blood vessel dilatation and decreased reactivity to noradrenaline.

The inhibitor of NOS, L-NAME was found to remove almost completely the depressing effect of LPS on the contraction of the abdominal bovine aorta,

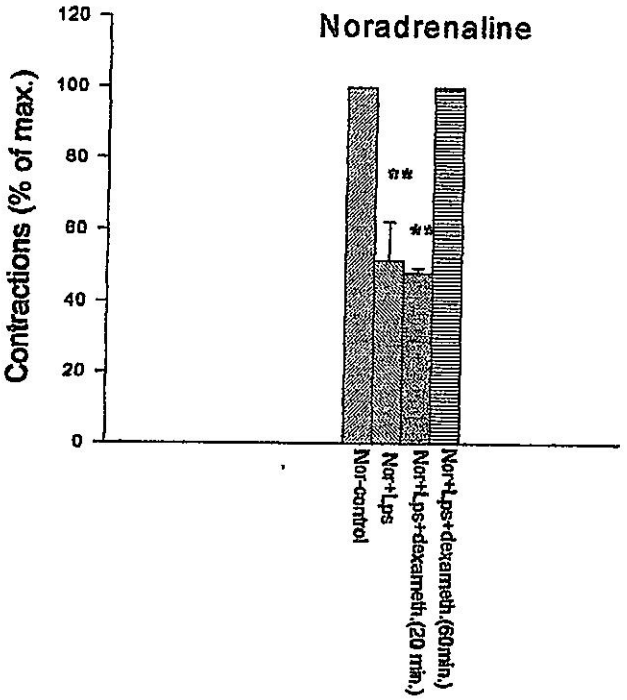

Figure 6. Efects of dexamethasone on the responsiveness to increasing concentations of noradrenaline of isolated bovine abdominal aorta, to the presence of LPS. Data are expressed as men + s.e.m. of (n-6) observations, **P<1.01 versus Nor-control.

induced by noradrenaline. Similar results have been obtained in other experimental animals such as the intrapulmonary arteries of neonatal piglets (Vilamor et al., 1995), rat mesenteric arteries (Martinez et al., 1996; Mitolo-Chieppa et al.., 1996) and ovine pulmonary arteries and veins (Nelson et al., 1996). L-NAME is krown to be an inhibitor of the constitutive and inducible NO-synthase. In chemical structure it is an analogue of L-arginine, an aminoacid that is a donor of NO, and as such L-NAME blocks the overproduction of NO induced by LPS (Bryant et al., 1995; Offner et al., 1995; Adams, 1995). The antagonistic activity of L-NAME is of a compettive nature in relation to the natural substrate L-arginine, as demonstrated in our experiment. When isolated bovine abdominal aorta was incubated in the presence of LPS, L-NAME and L-arginine, L-arginine antagonised the effect of L-NAME , thus allowing the contractile effect induced by noradrenaline on bovine abdominal aorta to be similar to that in the presence of LPS alone.

After an incubation period of 20 min. dexamethasone did not affect the depressing effect of LPS on the contraction of bovine abdominal aorta induced by noradrenaline. However, an incubation period of 60 min. enabled this glucocorticosteroid to inhibit iNOS, i. e. the synthesis of NO, thus allowing a much greater contractile effect of noradrenaline, in spite of the presence of

LPS. Similar results for dexamethasone on the isolated blood vessels were obtained by Villamor et al., (1995). They showed that dexamethasone, applied for an incubation period of 60 min., can normalize the LPS reduced reactivity of isolated intrapulmonary arteries of neonatal piglets to noradrenaline. On the basis of our results and those of other authors, dexamethasone can prevent the occurrence of hyporeactivity of blood vessels, which results from direct action of endotoxins.

The data obtained here show that the endotoxin LPS from E. coli significantly reduced the contractile effect of noradrenaline on isolated bovine abdominal aorta. The inhibitor of NOS N^G-nitro-L-arginine methyl ester (L-NAME) greatly decreased the depressing effect of LPS on the contractions of bovine abdominal aorta induced by noradrenaline, i. e. changed relaxation into contraction. Dexamethasone (as an inhibitor iNOS) after a long period of contact (incubation period of 60 min.) significantly increased the reactivity of the abdominal aorta to noradrenaline.

REFERENCES

1. *Adams, H. R.* 1995. Veterinary Pharmacology and Therapeutics, 7th ed. Iowa State University Press, Ames, Iowa, USA.
2. *Bryant, C. E., Perretti, M., Flower, R. J.,* 1998. Suppression by dexamethasone of inducible nitric oxide synthase protein expression in vivo: a possible role for lipocortin 1. Biochem. Pharmacol., 56, 279-285.
3. *Bryant, E. C., Allcock, H. G., Warner, D. T.,* 1995. Comparison of effects of chronic and acute administration of N^G-nitro-L-arginine methyl ester to the rat on inhibition of nitro oxide-mediated responses, Br. J. Pharmacol., 114, 1673-1679.
4. *Cannon, R. T., Mann, E. G., Baydoun, R. A.,* 1998. Mechanisme of acute vasodilatator response to bacterial lipopolysaccharide in the rat coronary microcirculation, Br. J. Pharmacol., 123, 637-644.
5. *Forstermann, U., Kleinert, H.* 1995. Nitro oxide synthase: expression and expressional control of the three isoforms. Naunyn Schmiedebergs. Arch. Pharmacol., 352, 351-364.
6. *Hoffman, B.B., Lefkawitz, R. J.* 1995. Catechoalamines, sympathomimetic drugs and adrenergic receptor antagonist. In Goodman and Gilmans's The Pharmacological Basis of Therapeutics. Eds., J. G., Hardman, L. E., Limbirg, P. B., Molinoff, R. W., Ruddon, McGraw-Hill, New York, London... Sydney, Tokyo, Toronto, str. 199-248.
7. *Isao, T., Yuichi, K., Nozomu, Y.* 1995. Effect of methylprednisolone on vasodialatation induced by lipopolysaccharide in human arteries. Shock, Molecular, Cellular and Systemic Pathobiological Aspects and Therapeutic Appreaches, O-39, Japan.
8. *Kumar, V., Cotran, S. R., Robbins, L. S.* 1997. Basic Pathology. Sixt ed, by W. B. Saunders Company, Philadelphia.
9. *Martinez, M. C., Muller, B., Staclet, J. C., Andriantsitohaina, R.* 1996. Alteration by lipopolysaccharide of the relationship between intracellular calcium levels and contraction in rat mesenteric artery, Br. J. Pharmacol., 118, 1212-1222.
10. *Mitalo-Chieppa, D., Serio, M., Potenza, M. A., Montagnari, M., Mansi, G. Pece, S. Jinilo, E. Stoclet, J. C.* 1996. Hyporeactivity of mesenteric vascular bed in endotoxin-treated rats. Eur. J. Pharmacol., 309, 175-182.
11. *Moncada, S., Palmer, R. M. J., Higgs, E. A.,* 1991. Nitric oxyde: physiology, pathophysiology, and pharmacology, Pharmacol. Rev., 43, 109-142.
12. *Nelson, S. H., Ehardt, J. S., Lingnau, W., Dehring, D. J., Traber., L., Traber, D.* 1996. Differential effects of prolonged septicemia on isolated pulmanary arteries and veins from sheep. Shoock, 5, 440-445.
13. *Offner, P. J., Robertson, F. M., Pruit, B. A. Jr.* 1995. Effects of nitric oxide synthese inhibition on regional blood fow in a porcine model endotoxic shock. J. Trauma, 39, 338-343.

14. *Parratt, J.* 1995. Nitric oxide in the cardovascular derangements of sepsis and endotoxamia. Shock. Molecular, Cellular and Systemic Phalthobiological Aspects and Therapeutic Approaches. S-1, Japan.

15. *Rees, D. D.* 1996. NO in septic shock. Therapeutic Perspectives. Recert Developments in Nitric Oxide. Conf. Document. London.

16. *Schulz, R., Triggle, R.* 1994, Role of NO in vascular smooth muscle and cardiac muscle function. Trends Pharmacol., 15, 255-259.

17. *Szabo, C., Mitchel, J. A., Thiermemann, C., Vane, J. R.* 1993c. Nitric oxide-mediated hyporeactivity to noradrenaline precedes the induction of nitric oxide synthase in endotoxin shock. Br. J. Pharmacol., 108, 786-792.

18. *Thiemermann, C.,* 1995. The role of nitric oxide in circulatory shock. Shook, Molecular. Celular and Systemic Pathobiological Aspects and Therapeutic Approaches, PL 1, Japan.

19. *Vilamor, E., Perez-Vizcaino, F., Teresa Ruiz, Leza, C. J., Moro M., Tamargo, J.* 1995. Group B. Sreptococcus and E. coli LPS-induced NO-dependent hyporesponsiveness of noradrenaline in isolated intrapulmonary arteries of neanatal piglets. Br. J. Pharmacol., 115, 261-266.

20. *Wu, C. C. Szabo, C. Chen, J. S., Thiermann, C., Vane, R. J.* 1994. Activation of soluble guanylyl cyclase by a factor other than nitric oxide or carbon monoxide contributes to the vascular hyporeactivity to vasoconstrictor agents in the aorta of rats treated with endotoxin. Biochem. Biophys. Res. Commun, 201, 436-442.

UTICAJ INHIBITORA NO-SINTAZE NA KONTRAKCIJU IZOLOVANE ABDOMINALNE AORTE GOVEČETA PROUZROKOVANU NORADRENALINOM U PRISUSTVU LPS-A

MIRJANA MILOVANOVIĆ i MILANKA JEZDIMIROVIĆ

SADRŽAJ

Poznato je da su endotoksini, lipopolisaharidi (LPS) iz gram-negativnih bakterija i da u organizmu sisara prouzrokuju ozbiljna oštećenja kardovaskularnog sistema, koja dominiraju septičkim šokom. U ovim eksperimentima, izvedenim na izolovanoj abdominalnoj aorti govečeta, ispitali smo uticaj LPS-a iz E. coli na kontraktilnost prouzrokovanu noradrenalinom. Takođe, nastojali smo da proučimo da li inhibitori NO-sintaze, L-NAME i deksametazon, utiču na moguće depresivno dejstvo LPS-a, na kontrakciju izolovane abdominalne aorte govečeta, prouzrokovanu noradrenalinom. Dobijeni rezultati pokazuju da LPS iz E. coli 055:B5 posle 4h inkubacije, izrazito značajno redukuje kontraktilni efekat noradrenalina, na izolovanoj abdominalnoj aorti govečeta. Inhibitor NO-sirtaze L-NAME, svojim specifičnim mehanizmom, antogonizuje depresivno dejstvo LPS-a, i tako omogućava noradrenalinu da dostigne maksimalan kontraktilni efekat na izolovanom krvnom sudu. Specifičnost dejstva L-NAME je potvrđena primenom L-arginina, koji je kao davaoc azotnog oksida, smanjio kontraktilni efekat noradrenalina u prisustvu LPS-a. Deksametazon, kao inhibitor iNOS, samo posle dužeg perioda inkubacije (60 minuta), značajno otklanja, odnosno antagonizuje depresivno dejstvo LPS-a, na kontrakcije izolovane abdominalne aorte govečeta prouzrokovane noradrenalinom.

Dobijeni rezultati pokazuju da depresivno dejstvo LPS-a na kontrakciju abdominalne aorte prouzrokovanu noradrenalinom, nastaje posredstvom L-arginin-NO sistema. Ovaj sistem ima značajnu ulogu u razvoju izrazite relaksacije glatkih mišića krvnih sudova u endotoksičkom šoku. Rana primena specifičnih inhibitora NO-sintaze i deksametazona može biti veoma korisna u sprečavanju progresivne hipotenzije u septičkom šoku.