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Hypertension alters the participation of contractile prostanoids and superoxide anions in lipopolysaccharide effects on small mesenteric arteries

Ana M. Briones [a], María J. Alonso [a], Raquel Hernanz [a], Silvia Tovar [a], Elisabet Vila [b], Mercedes Salaices [a,*]

[a] *Depto. de Farmacología y Terapéutica. Facultad de Medicina. Universidad Autónoma de Madrid. C/ Arzobispo Morcillo 4, 28029 Madrid, Spain*

[b] *Departament de Farmacologia i Terapéutica. Facultat de Medicina. Universitat Autònoma de Barcelona. Bellaterra 08193 Barcelona, Spain*

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Abstract

The involvement of cyclooxygenase-2 (COX-2)-derived products and superoxide anion in the effect of lipopolysaccharide in noradrenaline (NA)-induced contraction was investigated in small mesenteric arteries (SMA) from normotensive, Wistar Kyoto (WKY), and spontaneously hypertensive (SHR) rats. In WKY, lipopolysaccharide (10 μg/ml, 1 and 5 h) only inhibited the NA response (0.1–30 μM) in the presence of dexamethasone (1 μM), indomethacin (10 μM), the selective COX-2 inhibitor, NS 398 (10 μM), and the TXA_2/PGH_2 receptor antagonist, SQ 29,548 (10 μM) but not of superoxide dismutase (SOD, 100 U/ml). In SHR, lipopolysaccharide inhibited the NA response by itself; this inhibition was potentiated by dexamethasone, indomethacin, NS 398, SQ 29,548 and SOD. The effect of lipopolysaccharide plus indomethacin, NS 398 or SQ 29,548 was higher in SMA from WKY than SHR only after 1 h lipopolysaccharide incubation. N^G-nitro-L-arginine methyl ester (100 μM) and endothelium removal abolished the indomethacin-induced potentiatory effect of lipopolysaccharide in both strains. Endothelium removal also abolished the SOD potentiatory effect in SMA from SHR. Lipopolysaccharide increases COX-2 expression to a similar level in both strains and iNOS expression in a greater extent in SHR; these increases were reduced by dexamethasone. These results indicate: 1) lipopolysaccharide induces the endothelial production of contractile prostanoids from COX-2 in SMA, probably to compensate the increase in NO from iNOS; 2) the production of prostanoids in the presence of lipopolysaccharide

* Corresponding author. Tel.: +34-91-397-53-99; fax: +34-91-397-53-02.
E-mail address: mercedes.salaices@uam.es (M. Salaices).

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seems to be greater in normotensive than hypertensive rats only after lipopolysaccharide short incubation times; 3) endothelial production of O_2^- contributes to counteract depression of NA contraction caused by lipopolysaccharide only in SHR.

Keywords: Noradrenaline; Lipopolysaccharide; Hypertension; COX-2; Reactive oxygen species; Rat small mesenteric arteries

Introduction

Physiological vascular tone is modulated by various substances released from the endothelial layer including cyclooxygenase (COX) products and nitric oxide (NO). NO is derived from L-arginine by the enzyme NO synthase (NOS), while COX converts arachidonic acid to prostaglandins. There are two major isoforms of NOS and COX. The constitutively expressed isoforms of these enzymes (cNOS and COX-1) are found in several unstimulated cell types [1,2]. The inducible isoforms (iNOS and COX-2) are not normally expressed, but can be induced following appropriate stimulation with agents such as lipopolysaccharide (LPS) in different cell types such as endothelial or smooth muscle cells [1–3]. Anti-inflammatory steroids, including dexamethasone, inhibit the induction of iNOS and COX-2 *in vitro* and *in vivo* without apparent effect on the constitutive isoforms of the enzymes [1,4].

Hypotension and impaired responsiveness to vasoconstrictors are associated with vascular failure in human septic shock, as well as in experimental models in which LPS is administered both *in vivo* and *in vitro* [5,6]. Since NOS inhibitors can suppress both hypotension and vascular hyporesponsiveness to vasoconstrictors, it has been proposed that overproduction of NO via activation of iNOS plays an essential role in these effects [6,7]. However, the results on the involvement of COX products in the effects of LPS on vasoconstrictor responses, whether at early or long term, are still contradictory [8,9]. Several authors have questioned the possibility of a regulatory contribution of NO on the *in vivo* or *in vitro* production of prostanoids and suggest that inflammatory diseases are driven by both NO and prostaglandins [10,11]. In this sense, an increase in vasodilator prostaglandins like PGI_2 or PGE_2 has been reported after exposure to LPS, in both *in vivo* rats [12,13] and *in vitro* endothelial or smooth muscle cells treated with LPS [14,15]. In addition to vasodilator prostanoids, LPS may also induce vasoconstrictor eicosanoids production [8,9].

There are several studies indicating that the impairment in endothelium-dependent relaxations with hypertension might be due to the release of an endothelium-derived contractile factor from COX [16,17]. Furthermore, hypertension is associated with increased superoxide anion (O_2^-) production. This increased production has been found to be responsible for NO breakdown and is involved in the impaired endothelium-dependent responses associated with hypertension [18,19]. Additionally, an increase in O_2^- production in several models of endotoxic shock has also been described and seems to be involved in the endothelial dysfunction observed in this pathology [20,21].

Increased NO production and iNOS expression have been reported in LPS-treated arteries from hypertensive rats [22–24]. However, the involvement of prostanoids and reactive oxygen species in LPS effects and its alteration with hypertension are not well understood. Therefore, the aim of the present study was to evaluate the influence of COX-derived products and free radicals in the LPS effect in arteries from normotensive and hypertensive rats. We also analyzed COX-2 expression in both control and LPS-stimulated arteries from both strains.