Losartan and tempol treatments normalize the increased response to hydrogen peroxide in resistance arteries from hypertensive rats

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Objective **To analyse the role of angiotensin II, via AT_1 receptors, and oxidative stress in the mechanisms underlying the increased response to hydrogen peroxide (H_2O_2) of mesenteric resistance arteries from spontaneously hypertensive rats (SHRs).**

Methods **Arteries from normotensive and SHRs untreated or treated with the AT_1 receptor antagonist, losartan (15 mg/kg per day, 12 weeks), or with the superoxide dismutase analogue, tempol (1 mmol/l, 17 days), were used. Arteries were mounted in microvascular myographs for isometric tension recording; superoxide anion ($O_2^{\bullet-}$) production was evaluated by dihydroethidium fluorescence, thromboxane A_2 production by enzyme immunoassay and plasma nitrite levels by the Griess method.**

Results **H_2O_2 (1–100 μmol/l) induced higher contractile responses in mesenteric resistance arteries from hypertensive than normotensive rats. In SHRs, losartan and tempol treatments induced the following effects: normalized the increased H_2O_2 contractile responses observed; modified neither the inhibitory effects of the cyclooxygenase inhibitor, indomethacin [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1-H-indole-3-acetic acid] (1 μmol/l), and the thromboxane A_2/prostaglandin H_2 receptor antagonist, SQ 29 548 (1 μmol/l), on H_2O_2 contraction, nor the increase in thromboxane A_2 production in response to H_2O_2; abolished the increased vascular $O_2^{\bullet-}$ production; increased both the potentiatory effect of the nitric oxide inhibitor, *N*(G)-nitro-L-arginine methyl ester (100 μmol/l), on H_2O_2 responses and the acetylcholine-induced relaxation. Moreover, losartan treatment abolished the effect of the $O_2^{\bullet-}$ scavenger, tiron (1 mmol/l), on H_2O_2 responses and increased plasma nitrite levels.**

Conclusion **Nitric oxide removal by an excessive $O_2^{\bullet-}$ production, probably from an upregulated renin–angiotensin system, participates in the increased response to H_2O_2 in mesenteric resistance arteries from SHRs.**

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Abbreviations: Ang II, angiotensin II; COX, cyclooxygenase; H_2O_2, hydrogen peroxide; KHS, Krebs–Henseleit solution; MRAs, mesenteric resistance arteries; $O_2^{\bullet-}$, superoxide anion; ROS, reactive oxygen species; SHR, spontaneously hypertensive rats; TX, thromboxane; VSMCs, vascular smooth muscle cells; WKY, Wistar Kyoto

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Introduction

It is well known that reactive oxygen species (ROS) play an important role in the development of cardiovascular diseases, including hypertension. This is due, in large part, to excessive production of oxidants, decreased nitric oxide bioavailability and decreased antioxidant capacity in the vasculature [1]. Increased plasma levels of hydrogen peroxide (H_2O_2) have been described in hypertensive patients [2], and it has been suggested as a mediator of vascular structural and functional alterations observed in hypertension [1]. The main source of H_2O_2 is the dismutation of superoxide anion ($O_2^{\bullet-}$) by superoxide dismutase (SOD). However, H_2O_2 can be produced directly by other cellular enzymes such as nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidase [3] and xanthine oxidase [4]. Moreover, H_2O_2 can produce $O_2^{\bullet-}$ by activation of NAD(P)H oxidase, thus creating a vicious circle associated with oxidative stress-induced vascular damage in hypertension [5,6]. H_2O_2 is more stable than $O_2^{\bullet-}$, easily diffuses across cellular membranes and is considered an important second messenger in smooth muscle cell signalling and hypertrophy, although its role in vascular tone is controversial [7]. We have previously described that in rat mesenteric resistance arteries (MRAs), H_2O_2 induces a contractile response that is greater in vessels from hypertensive than normotensive rats [6]. This contractile response was mainly mediated by cyclooxygenase (COX)-1-derived thromboxane A_2 (TXA_2) in arteries from normotensive

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