Hypertension Increases Contractile Responses to Hydrogen Peroxide in Resistance Arteries through Increased Thromboxane A₂, Ca²⁺, and Superoxide Anion Levels

Ana Belén García-Redondo, Ana María Briones, Amada Elia Beltrán, María Jesús Alonso, Ulf Simonsen, and Mercedes Salaices

Departamento de Farmacología, Facultad de Medicina, Universidad Autónoma de Madrid, Madrid, Spain (A.B.-G.-R., A.M.B., A.E.B., M.S.); Departamento de Ciencias de la Salud III, Universidad Rey Juan Carlos, Alcorcón, Madrid, Spain (M.J.A.); and Department of Pharmacology University of Aarhus, Aarhus C, Denmark (U.S.)

Received August 1, 2008; accepted September 24, 2008

ABSTRACT

This study investigated the mechanisms underlying the response to hydrogen peroxide (H₂O₂) in mesenteric resistance arteries from spontaneously hypertensive rats (SHRs) and normotensive Wistar Kyoto (WKY) rats. Arteries were mounted in microvascular myographs for isometric tension recording and for simultaneous measurements of intracellular Ca²⁺ concentration ([Ca²⁺]i), superoxide anion (O₂⁻) production was evaluated by dihydroethidium fluorescence and confocal microscopy, and thromboxane A₂ (TXA₂) production was evaluated by enzyme immunoassay. H₂O₂ production was greater in SHRs than in WKY rats. The TXA₂ analog, U46619 [9,11-di-deoxy-11α,9α-epoxymethano prostaglandin F₂α (0.1 nM–1 μM)], also increased O₂⁻ production in SHR vessels. H₂O₂-induced TXA₂ and O₂⁻ production was diminished by SC-58560 [5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-trifluoromethyl pyrazole] (1 μM); the TXA₂ synthase inhibitor, furegrelate [5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-trifluoromethyl pyrazole] (1 μM); and the TXA₂/prostaglandin H₂ receptor antagonist, SQ 29,548 ([1S-[1.α,2.α,(Z),3.α,4.α]]-7-[3-[2-[(phenylamino) carbonyl] hydrazino] methyl]-7-oxa-bicyclo[2.2.1]hept-2-yl]-5-hep-tenoic acid) (1 μM) abolished H₂O₂ contraction in arteries from WKY rats but only reduced it in SHRs. The O₂⁻ scavenger, tiron (4,5-dihydroxy-1,3-benzenedisulfonic acid disodium salt) (1 mM), and the NADPH oxidase inhibitor, apocynin (4'-hydroxy-3'-methoxyacetophenone) (0.3 mM), decreased H₂O₂ contraction in arteries from SHRs but not in WKY rats. H₂O₂-induced TXA₂ and O₂⁻ production that was greater in SHRs than in WKY rats. The TXA₂ analog, U46619 [9,11-di-deoxy-11α,9α-epoxymethano prostaglandin F₂α (0.1 nM–1 μM)], also increased O₂⁻ production in SHR vessels. H₂O₂-induced TXA₂ production was decreased by SC-58560. H₂O₂-induced O₂⁻ production was decreased by tiron, apocynin, and SQ 29,548. In conclusion, the enhanced H₂O₂ contraction in resistance arteries from SHRs seems to be mediated by increased TXA₂ release from COX-1 followed by elevations in vascular smooth muscle [Ca²⁺]i levels and O₂⁻ production. This reveals a new mechanism of oxidative stress-induced vascular damage in hypertension.

Reactive oxygen species (ROS) like superoxide anion (O₂⁻) and hydrogen peroxide (H₂O₂) have been suggested as mediators of vascular structural and functional alterations observed in hypertension (Lacy et al., 2000; Paravicini and Touyz, 2006; Alvarez et al., 2007). Several sources of O₂⁻ have been described. Among them, xanthine oxidase, uncoupled nitric-oxide synthase, and cyclooxygenase (COX) can produce O₂⁻ in different conditions (Touyz, 2003). However, it is well established that at the vascular level, NADPH oxidase is the main source of O₂⁻ (Touyz, 2003; Lyle and Griendling, 2006). Dismutation of O₂⁻ by superoxide dismutase produces H₂O₂, a main source of O₂⁻ (Touyz, 2003; Lyle and Griendling, 2006). Dismutation of O₂⁻ by superoxide dismutase produces H₂O₂, a