UltraRapid Communications

Vascular Superoxide Production by NAD(P)H Oxidase Association With Endothelial Dysfunction and Clinical Risk Factors

Tomasz J. Guzik, Nick E.J. West, Edward Black, Denise McDonald, Chandi Ratnatunga, Ravi Pillai, Keith M. Channon

Abstract—Superoxide anion plays important roles in vascular disease states. Increased superoxide production contributes to reduced nitric oxide (NO) bioactivity and endothelial dysfunction in experimental models of vascular disease. We measured superoxide production by NAD(P)H oxidase in human blood vessels and examined the relationships between NAD(P)H oxidase activity, NO-mediated endothelial function, and clinical risk factors for atherosclerosis. Endothelium-dependent vasorelaxations and direct measurements of vascular superoxide production were determined in human saphenous veins obtained from 133 patients with coronary artery disease and identified risk factors. The predominant source of vascular superoxide production was an NAD(P)H-dependent oxidase. Increased vascular NAD(P)H oxidase activity was associated with reduced NO-mediated vasorelaxation. Furthermore, reduced endothelial vasorelaxations and increased vascular NAD(P)H oxidase activity were both associated with increased clinical risk factors for atherosclerosis. Diabetes and hypercholesterolemia were independently associated with increased NADH-dependent superoxide production. The association of increased vascular NAD(P)H oxidase activity with endothelial dysfunction and with clinical risk factors suggests an important role for NAD(P)H oxidase–mediated superoxide production in human atherosclerosis. The full text of this article is available at http://www.circresaha.org. (Circ Res. 2000;86:e85–90.)

Key Words: atherosclerosis ■ endothelium ■ superoxide ■ nitric oxide ■ diabetes

Two Distinct Congenital Arrhythmias Evoked by a Multidysfunctional Na⁺ Channel

Marieke W. Veldkamp, Prakash C. Viswanathan, Connie Bezzina, Antonius Baartscheer, Arthur A.M. Wilde, Jeffrey R. Balser

Abstract—The congenital long-QT syndrome (LQT3) and the Brugada syndrome are distinct, life-threatening rhythm disorders linked to autosomal dominant mutations in SCN5A, the gene encoding the human cardiac Na⁺ channel. It is believed that these two syndromes result from opposite molecular effects: LQT3 mutations induce a gain of function, whereas Brugada syndrome mutations reduce Na⁺ channel function. Paradoxically, an inherited C-terminal SCN5A mutation causes affected individuals to manifest electrocardiographic features of both syndromes: QT-interval prolongation (LQT3) at slow heart rates and distinctive ST-segment elevations (Brugada syndrome) with exercise. In the present study, we show that the insertion of the amino acid 1795insD has opposite effects on two distinct kinetic components of Na⁺ channel gating (fast and slow inactivation) that render unique, simultaneous effects on cardiac excitability. The mutation disrupts fast inactivation, causing sustained Na⁺ current throughout the action potential plateau and prolonging cardiac repolarization at slow heart rates. At the same time, 1795insD augments slow inactivation, delaying recovery of Na⁺ channel availability between stimuli and reducing the Na⁺ current at rapid heart rates. Our findings reveal a novel molecular mechanism for the Brugada syndrome and identify a new dual mechanism whereby single SCN5A mutations may evoke multiple cardiac arrhythmia syndromes by influencing diverse components of Na⁺ channel gating function. The full text of this article is available at http://www.circresaha.org. (Circ Res. 2000;86:e91-e97.)

Key Words: Na⁺ channel ■ inactivation ■ long-QT syndrome ■ Brugada syndrome

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