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Novel isoforms of NADPH-oxidase in cerebral vascular control

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Abstract

Reactive oxygen species (ROS) are thought to play an important role in the initiation and progression of a variety of vascular diseases. Furthermore, accumulating evidence indicates that ROS may also serve as important cell signalling molecules for the regulation of normal vascular function. Recently, a novel family of proteins (Nox1, 2 and 4) that act as the catalytic subunit of the superoxide (O_2^-) producing enzyme NADPH-oxidase has been discovered in vascular cells. There is now preliminary evidence suggesting that NADPH-oxidase-derived ROS may serve as a physiological vasodilator mechanism in the cerebral circulation. Moreover, the activity of NADPH-oxidase is profoundly greater in cerebral versus systemic arteries. Studies have shown that Nox1, Nox2 (also known as gp91phox) and Nox4 are all expressed in cerebral arteries, suggesting that multiple isoforms of NADPH-oxidase may be important for ROS production by cerebral arteries. Enhanced NADPH-oxidase activity is associated with several vascular-related diseases, including hypertension, stroke, subarachnoid haemorrhage and Alzheimer's dementia; however, the consequences of this for cerebral vascular function are controversial. For example, there is some evidence suggesting that NADPH-oxidase-derived O_2^- may play a role in endothelial dysfunction of cerebral arteries and a subsequent rise in cerebral vascular tone, associated with hypertension. However, activation of NADPH-oxidase elicits cerebral vasodilatation in vivo, and this mechanism is enhanced in chronic hypertension. While further supportive evidence is needed, it is an intriguing possibility that NADPH-oxidase-derived ROS may play a protective role in regulating cerebral vascular tone during disease.

Keywords: NADPH-oxidase; Cerebral vascular; Hydrogen peroxide; Superoxide; Hypertension

Abbreviations: Aβ, amyloid-β peptide; ACE, angiotensin-converting enzyme; ACh, acetylcholine; AD, Alzheimer's disease; AEBSF, aminoethylbenzenesulfono fluoride; APP, amyloid precursor protein; CBF, cerebral blood flow; cGMP, guanosine monophosphate; DETCA, diethyldithiocarbamate; DPI, diphenyleneiodonium; EDHF, endothelium-derived hyperpolarizing factor; EDRF, endothelium-derived relaxing factor; eNOS, endothelial nitric oxide synthase; FAD, flavin adenine nucleotide; H_2O_2, hydrogen peroxide; $NO^{\bullet}$, nitric oxide; NOS, nitric oxide synthases; NoxA1, NOX activator 1; NoxO1, NOX organizer 1; O_2^-, superoxide; $OH^{\bullet}$, hydroxyl; $ONOO^-$, peroxynitrite; PEG-SOD, polyethylene glycol superoxide dismutase; ROS, reactive oxygen species; SOD, superoxide dismutases; SOD1, CuZn-containing cytosolic superoxide dismutase; SOD2, Mn-containing superoxide dismutase; SOD3, CuZn-containing extracellular superoxide dismutase; TEA, tetraethylammonium; TPCK, tosylphenylalanylchoromethane; VSM, vascular smooth muscle.

Contents

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1. Introduction

Classically, reactive oxygen species (ROS), such as superoxide (O_2^-), were regarded as accidental and potentially toxic by-products of cellular metabolism, whereby it would be important for cells to rapidly 'detoxify' these products before they cause damage. Indeed, over the last few decades it has been established that when generated in excess ROS can react non-specifically and rapidly with biomolecules causing cellular damage such as DNA mutations, lipid peroxidation and protein oxidation. While this mechanism is still recognized as being important in many vascular diseases, it is now also evident that ROS exert more subtle effects on vascular function and structure during disease (e.g. vascular smooth muscle (VSM) hypertrophy and hyperplasia). Furthermore, the discovery that enzymes, whose sole purpose is to generate ROS, are not only expressed but are functionally active in vascular cells under physiological conditions, suggests that the generation of ROS is intentional and potentially important for normal vascular function. Indeed, recent studies have reported that low levels of ROS are generated constitutively in a controlled manner, and can act as important cell signalling molecules, affecting many aspects of vascular function such as VSM cell proliferation and tone (Griendling et al., 2000; Cai, 2005b; Miller et al., 2005a).

The O_2^- generating enzyme, NADPH-oxidase, was first identified and characterized in phagocytic cells (Babior et al., 2002). Recently, novel isoforms of this 'classical' NADPH-oxidase, differing from each other primarily in the nature of the 'Nox' catalytic subunit they utilise, have been discovered in vascular cells. Furthermore, it is now recognized that these enzymes are likely to be important physiological generators of ROS in both cerebral and systemic vasculatures (Griendling et al., 1994; Miller et al., 2005a). To date, a physiological role has been established for NADPH-oxidase-derived ROS in regulating VSM cell growth (Suh et al., 1999), in vascular oxygen sensing mechanisms (Wolin et al., 1999, 2005) and in central neural regulation of the cardiovascular system (Zimmerman et al., 2002, 2004; Wang et al., 2004). Furthermore, recent studies have raised the possibility that NADPH-oxidase-derived ROS may serve as cerebral vasodilators (Didion & Faraci, 2002; Paravicini et al., 2004; Park et al., 2004c; Miller et al., 2005a; Paravicini et al., in press). Enhanced NADPH-oxidase activity is associated with several vascular diseases, such as hypertension and stroke (Walder et al., 1997; Green et al., 2001; Shin et al., 2002); however, the overall effects of this for cerebral vascular function are still unclear.

2. Characteristics of cerebral arteries

The brain has minimal storage of energy sources, making it exceptionally sensitive to interruptions to its blood supply (Sokoloff, 1997). Indeed, if blood flow to the brain is interrupted, a loss of consciousness can occur within seconds and irreversible neuronal damage within minutes (Sokoloff, 1997). It is not surprising, therefore, that the cerebral circulation is a highly specialised vascular bed with a number of unique