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NOXious signaling in pain processing

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ABSTRACT

Chronic pain affects millions of people and often causes major health problems. Accumulating evidence indicates that the production of reactive oxygen species (ROS), such as superoxide anion or hydrogen peroxide, is increased in the nociceptive system during chronic inflammatory and neuropathic pain, and that ROS can act as specific signaling molecules in pain processing. Reduction of ROS levels by administration of scavengers or antioxidant compounds attenuated the nociceptive behavior in various animal models of chronic pain. However, the sources of increased ROS production during chronic pain and the role of ROS in pain processing are poorly understood. Current work revealed pain-relevant functions of the Nox family of NADPH oxidases, a group of electron-transporting transmembrane enzymes whose sole function seems to be the generation of ROS. In particular, significant expression of the Nox family members Nox1, Nox2, and Nox4 in various cells of the nociceptive system has been discovered. Studies using knockout mice suggest that these Nox enzymes specifically contribute to distinct signaling pathways in chronic inflammatory and/or neuropathic pain states. Accordingly, targeting Nox1, Nox2, and Nox4 could be a novel strategy for the treatment of chronic pain. Currently selective inhibitors of Nox enzymes are being developed. Here, we introduce the distinct roles of Nox enzymes in pain processing, we summarize recent findings in the understanding of ROS-dependent signaling pathways in the nociceptive system, and we discuss potential analgesic properties of currently available Nox inhibitors.

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Contents

1. Introduction

Painful thermal, chemical or mechanical stimuli are recognized by a subpopulation of primary afferent neurons. Upon activation, these neurons transmit the nociceptive signal to the dorsal horn of the spinal cord. There the nociceptive signals are sorted and sent to supraspinal sites giving rise to the pain sensation and response. In contrast to perception of nociceptive painful stimuli, tissue damage (inflammatory pain) or injury to the somatosensory nervous system (neuropathic pain) normally results in hypersensitivity. The response to noxious stimuli can be amplified (hyperalgesia), normally innocuous stimuli may evoke pain perception (allodynia), and pain in absence of any stimulus (spontaneous pain) can arise. Moreover, the hypersensitivity can

Abbreviations: DRG, dorsal root ganglion; DPI, diphenylene iodonium; DUOX, dual oxidase; GSH, glutathione; GTP, guanosine triphosphate; IL, interleukin; LTP, long-term potentiation; MAP, mitogen-activated kinase; NMDA, N-methyl-D-aspartate; NADPH, nicotinamide adenine dinucleotide phosphate; Nox, NADPH oxidase; NOXA1, Nox activator 1; NOXO1, Nox organizer 1; PBN, phenyl-N-tert-butylnitrone; PDI, protein disulfide isomerase; PKC, protein kinase C; PTP, protein tyrosine phosphatase; ROS, reactive oxygen species; SOD, superoxide dismutase; TBHP, tert-butyl hydroperoxide; TEMPOL, 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxy; Tks4/5, tyrosine kinase substrate with 4/5 SH3 domains; TRP, transient receptor potential.

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persist long after the initial injury is resolved, thereby causing major health problems (Schmidtko et al., 2009, 2010). In fact, chronic pain is an enormous medical burden, with up to 20% of the adult population suffering (Tracey & Dickenson, 2012), and more than half of chronic pain patients report inadequate pain relief with currently available drugs (Gold & Gebhart, 2010). Therefore, elucidating the mechanisms underlying pain hypersensitivity is a rational strategy for the development of novel analgesic drugs.

Pain hypersensitivity is mediated by multiple alterations in the periphery as well as in the central nervous system (for review see Basbaum et al., 2009; Gold & Gebhart, 2010; Kuner, 2010). Accumulating evidence suggests that reactive oxygen species (ROS) essentially contribute to the development of pain hypersensitivity. In general, ROS are generated as intermediates in reduction–oxidation (redox) reactions resulting in the conversion of O_2 into H_2O. ROS are either free radicals (e.g., superoxide anion [$\cdot O_2^-$]) or nonradical derivatives of O_2 (e.g., hydrogen peroxide [H_2O_2]) (Paravicini & Touyz, 2008) (Fig. 1). Due to their highly reactive nature, ROS can potentially damage nucleic acids, proteins and lipids, especially at high concentrations (Wang & Michaelis, 2010). However, recent studies revealed that ROS at physiological concentrations mediate reversible regulatory processes and serve as functional messenger molecules, possibly fulfilling a large range of physiological and pathophysiological functions including pain processing (Sorce & Krause, 2009). The specific functions of ROS are seemingly mediated by direct action of superoxide and hydrogen peroxide, and in an indirect manner by the reactive nitrogen species peroxynitrite that is produced by reaction of superoxide with nitric oxide (Salvemini et al., 2011; Tegeder et al., 2011; Little et al., 2012) (Fig. 1).

The essential contribution of ROS to pain processing is reflected by several lines of evidence. For example, intrathecal injection of the ROS donor tert-butyl hydroperoxide (TBHP) induced mechanical hyperalgesia (Schwartz et al., 2008; Lu et al., 2011; Yowtak et al., 2011) and inactivation of the antioxidative enzymes superoxide dismutase (SOD) 1 and 2 was associated with an increased pain behavior (Schwartz et al., 2009; Berger et al., 2011), suggesting that elevated spinal ROS levels are sufficient to induce pain behaviors in rodents. Notably, many studies demonstrated a profound inhibition of neuropathic and inflammatory pain behaviors after reducing endogenous ROS levels by delivery of free radical scavengers and SOD mimetics. For example, systemic or intrathecal administration of the free radical scavenger phenyl-N-tert-butylnitrone (PBN) and the SOD mimetic 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxy (TEMPOL) inhibited the pain behavior in different animal models of neuropathic pain (Tal, 1996; Kim et al., 2004; Gao et al., 2007; Siniscalco et al., 2007; Kim et al., 2009; Tanabe et al., 2009; Fidanboylu et al., 2011; Yowtak et al., 2011; Lee et al., 2012). PBN and TEMPOL were also effective in inhibiting inflammatory pain behavior induced by injection of different proinflammatory compounds into a hindpaw (Hacimuftuoglu et al., 2006; Khattab, 2006; Gao et al., 2007; Lee et al., 2007; Schwartz et al., 2008). Other drugs that reduce endogenous ROS levels demonstrated antinociceptive effects in animal models of either neuropathic or inflammatory pain. For example, a combination of vitamins C and E that exerts synergistic antioxidative effects of both vitamins inhibited the neuropathic pain behavior after peripheral nerve injury and ameliorated the p38 MAP kinase activation in the nociceptive system. In contrast, persistent inflammatory pain behaviors were not affected by the vitamin combination (Lu et al., 2011). These data indicate that some antioxidants may inhibit nociceptive processing only at specific pain states, pointing to specific ROS-dependent processing during neuropathic and inflammatory pain.

The question arises which endogenous sources produce ROS during pain processing. In general, there are numerous potential sources of ROS within cells, including mitochondria (in particular, complexes I and III of the electron transport chain), xanthine oxidase, cyclooxygenases, cytochrome P450 monooxygenases, lipoxygenases, uncoupled endothelial NO synthase, and nicotinamide adenine dinucleotide phosphate (NADPH) oxidases. The latter comprise a family of enzymes that rely on NADPH for their activity. The primary catalytic function of NADPH oxidases is the regulated generation of ROS (Finkel, 2011), in contrast to the other ROS sources which produce ROS either as a by-product of their normal catalytic activity or as a result of aberrant functioning in disease. While the expression of NADPH oxidases was initially thought to be confined to phagocytic cells, it is now clear that they are widely expressed and have crucial roles in various physiological and pathophysiological processes (Drummond et al., 2011). Herein, we will review the emerging functions of NADPH oxidases in pain processing and highlight their distinct contribution to different types of persistent pain.

2. Nox enzymes generate reactive oxygen species during pain processing

2.1. Nox2

NADPH oxidases (Nox) are membrane-bound enzyme complexes that transport electrons from NADPH over the membrane to reduce molecular oxygen to superoxide anions or hydrogen peroxide. The family of NADPH oxidases consist of seven members, Nox1 to Nox5 as well as DUOX1 and DUOX2, (the latter two termed dual oxidases [DUOX] due to both a peroxidase like domain and a Nox like domain (Edens et al., 2001)), which show distinct expression patterns and are regulated differently (for review, see Bedard & Krause, 2007). Nox2, the first described NADPH oxidase (also designated as gp91^{phox}) and catalytic subunit of the phagocyte NADPH oxidase, was cloned in the 1980s (Royer-Pokora et al., 1986; Teahan et al., 1987). Meanwhile it has been found to be expressed in a broad spectrum of cells and tissues including the central nervous system (Bedard & Krause, 2007; Sorce & Krause, 2009; Gao et al., 2012). Nox2 activity is tightly controlled by the regulatory cytosolic subunits p40^{phox}, p47^{phox}, p67^{phox}, and the small guanosine triphosphate (GTP)ase Rac. Upon phosphorylation of p47^{phox}, the resulting conformational change

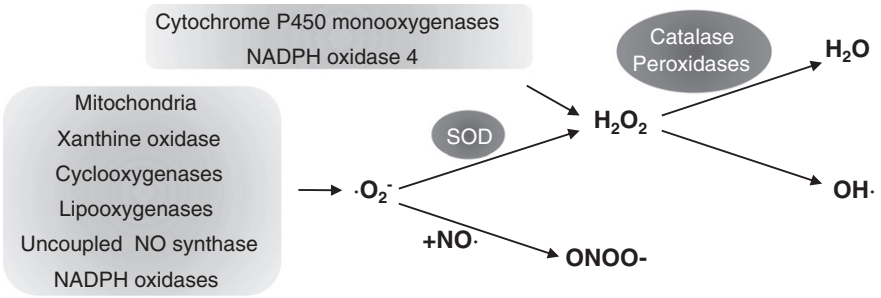

Fig. 1. Overview of the ROS metabolism. Superoxide anion ($\cdot O_2^-$) can be converted to hydrogen peroxide (H_2O_2), a process which is catalyzed by SOD. Hydrogen peroxide is then decomposed by various enzymes to water (H_2O) or can form hydroxyl radicals (OH·), caused by a one-electron reduction. Furthermore, superoxide anion can react with nitric oxide (NO·) to form the reactive nitrogen species peroxynitrite ($ONOO^-$).

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