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Mini Review

Positive oxidative stress in aging and aging-related disease tolerance ☆

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ABSTRACT

It is now well established that reactive oxygen species (ROS), reactive nitrogen species (RNS), and a basal level of oxidative stress are essential for cell survival. It is also well known that while severe oxidative stress often leads to widespread oxidative damage and cell death, a moderate level of oxidative stress, induced by a variety of stressors, can yield great beneficial effects on adaptive cellular responses to pathological challenges in aging and aging-associated disease tolerance such as ischemia tolerance. Here in this review, I term this moderate level of oxidative stress as positive oxidative stress, which usually involves imprinting molecular signatures on lipids and proteins via formation of lipid peroxidation by-products and protein oxidation adducts. As ROS/RNS are short-lived molecules, these molecular signatures can thus execute the ultimate function of ROS/RNS. Representative examples of lipid peroxidation products and protein oxidation adducts are presented to illustrate the role of positive oxidative stress in a variety of pathological settings, demonstrating that positive oxidative stress could be a valuable prophylactic and/or therapeutic approach targeting aging and aging-associated diseases.

Contents

Introduction

Production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) is part of normal aerobic cellular metabolism [1–5]. While RNS generally originate from nitric oxide synthases, ROS can be generated by a variety of enzymes and metabolic pathways, including mitochondrial complexes I–III [6–9] in the electron transport chain, dihydrolipoamide dehydrogenase in the α-keto acid dehydrogenase complexes [10–14], NADPH oxidase [15,16], xanthine oxidase [17,18], monoamine oxidase [19], and cytochrome P450 proteins [20]. All of these systems may result in oxidative stress under appropriate conditions. Although basal levels of ROS/RNS are

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indispensible for redox signaling and cell survival [21,22], high levels of ROS/RNS would be detrimental to cells and have been thought to contribute to aging and the pathogenesis of numerous aging-related diseases [22,23]. On the other hand, a moderate level of oxidative stress, reflected by a moderate level of ROS/RNS production, could be induced and modulated to produce an adaptive cellular response that is beneficial for cell survival [22–27].

Oxidative stress is a situation whereby cellular levels of ROS or RNS overwhelm the cellular antioxidant capacities [20]. This condition, when severe, usually leads to extensive modifications or damage to macromolecules including DNA, lipids and proteins [28,29]. Collectively, these damaged macromolecules, when beyond the cell's reparative and degradative activities, can eventually induce cell death and tissue injury [22,25]. Nonetheless, increasing evidence has now established that many protein oxidation or lipid oxidation products can be beneficial for cell survival [29–32]. These oxidation products are usually caused by a moderate level of oxidative stress, which is termed here as positive oxidative stress. This is the type of oxidative stress that can induce or is part of an adaptive response that protects cells against subsequent severe challenges that otherwise would trigger widespread oxidative damage and cell death [23,27].

In order to create a positive oxidative stress condition, it is necessary to stress cells with a stressor [22,27]. Many stressors, when used at appropriate dosages, can elicit a moderate or non-lethal level of oxidative stress in the absence of cytotoxicity and cell death [27]. Nonetheless, it should be pointed out that if used at higher dosages; almost all stressors will inevitably yield toxicity that leads to cell death.

The best examples of positive oxidative stress would be ischemic tolerance including preconditioning and postconditioning, which are clinically-relevant approaches applied in a variety of animal models for protection of tissues against ischemia-induced injuries [33–35]. It has been well-demonstrated that a variety of stressors, such as, mitochondrial electron transport chain inhibitors [36], hypoxia [37], hyperoxia [38,39], hyperthermia [40] and hypothermia [41], as well as short episodes of ischemia [42] can induce positive oxidative stress via a transiently increased ROS production that is involved in an adaptive response for prophylactic purposes (Table 1) [43–49]. Accordingly, many studies have shown that antioxidants administered prior to or at the onset of preconditioning or postconditioning induction, can abolish the preconditioning or postconditioning effect [34,35,50,51], thus demonstrating that ROS and oxidative stress are essential for preconditioning or postconditioning to take effect [52–54]. Interestingly, the effects of preconditioning and postconditioning are only evident in severe pathological challenges such as an extended period of ischemia or reperfusion.

So how does positive oxidative stress work? As ROS and RNS are short-lived molecules, they themselves cannot impart a persistent beneficial effect [22]. It is thus believed that the targets of ROS and RNS would serve as molecular signatures [23] that relay and extend the beneficial effects of positive oxidative stress [22]. These molecular signatures are those of ROS/RNS modified oxidative products such as lipid peroxidation by-products and protein oxidation adducts. Chemically, numerous protein oxidative modifications involved in positive oxidative stress are reversible such as disulfide formation [55–60], *S*-glutathionylation [61–64], *S*-sulfenation [65–67], and *S*-nitrosylation [68–71]. These enhanced modifications usually play regulatory roles in protein function and thus can elicit great protective effects against cell death induced by a variety of severe stress conditions. As has been reported, all these reversible cysteine modifications can occur under basal conditions [72–79]. In the absence of positive oxidative stress, however, these basal level modifications may have no apparent protective effects owing to their low abundance.

Herein to demonstrate the role of positive oxidative stress in aging and aging-associated diseases, I would like to present a few selected representative examples of oxidative molecular signatures that are beneficial for cell survival. These examples include lipid peroxidation products and protein oxidation adducts.

Positive effect of lipid peroxidation products

Lipid peroxides in hemoglobin-modified low density lipoprotein are beneficial for cell survival

Hemoglobin (Hb) can modify low density lipoproteins (LDL), and lipid oxidation of the latter is usually linked to pathogenesis of atherosclerosis [31]. However, while hemoglobin-binding of LDL renders the complex (Hb–LDL) highly susceptible to lipid peroxidation, such oxidation products are not cytotoxic [31]. The reason for this is that oxidized Hb–LDL could induce HO-1 (hemeoxygenase-1) expression, likely via the activation of the Nrf2 transcription factor [80]. Notably, when oxidized Hb–LDL was reduced by ebselen, HO-1 induction was inhibited [31]. Therefore, oxidized Hb–LDL can exhibit a beneficial effect via HO-1 induction.

Table 1
Popular stressors known to induce positive oxidative stress. Many of these stressors have been studied in the context of tissue ischemic tolerance.

Stressors	Beneficial effects	Selected references
3-Nitropropionic acid	Complex II inhibitor, ischemic tolerance	[83–85]
Rotenone	Complex I inhibitor, ischemic tolerance	[86]
Antimycin A	Complex III inhibitor, ischemic tolerance	[86]
Diazoxide	kATP channel opener, ischemic tolerance	[87]
Cyanide	Complex IV inhibitor, ischemic tolerance	[53]
Cobalt chloride	Chemical hypoxia/HIF-1 activation	[88,89]
Carbon monoxide	ROS-mediated prevention of apoptosis	[61]
Isoflurane	Induction of pre- and postconditioning	[90,91]
Short episodes of ischemia	Ischemic tolerance	[92–94]
Hypoxia/intermittent hypoxia	Ischemic tolerance	[37,95]
Hyperoxia	Ischemic tolerance	[38,39]
Hyperthermal stress	Ischemic tolerance	[40]
Hypothermal stress	Ischemic tolerance	[41]
Remote preconditioning	Ischemic tolerance	[96–98]
Physical exercise	Production of beneficial ROS	[50]
Hydrogen peroxide	Ischemic tolerance	[99,100]
Ozone	Ischemic tolerance	[101,102]

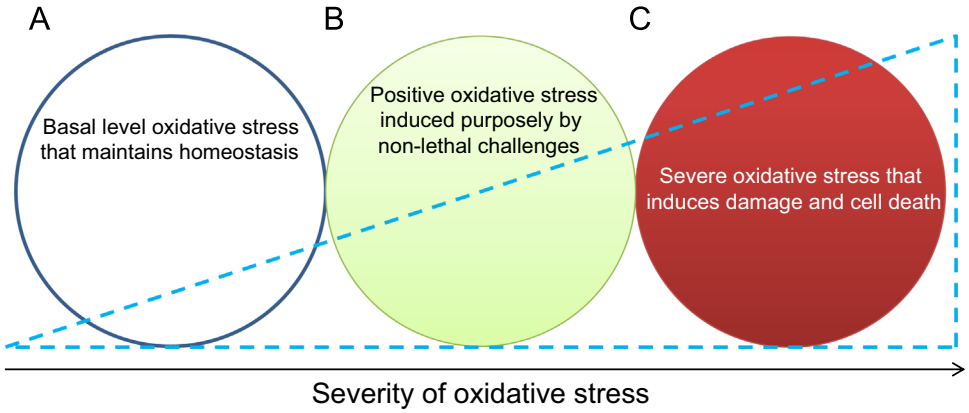

Fig. 1. Levels of cellular oxidative stress and their differential effects. (A) basal level oxidative stress that is essential for cell survival and homeostasis; (B) positive oxidative stress that can be induced by a variety of non-lethal challenges that often induce protein oxidative modifications; (C) Severe oxidative stress that induces damage and cell death.

Beneficial effect of a cholesterol oxidation product

24-*S*-hydroxycholesterol (24-SOHC) is endogenously produced in the brain and plays an important role in brain cholesterol homeostasis. Okabe et al. recently showed that 24-SOHS could elicit an adaptive response in human neuroblastoma SH-SY5Y cells [81]. They found that cells treated with 24-SOHC at non-lethal levels could significantly attenuate cell death induced subsequently by 7-keto cholesterol (7KC). Furthermore, the attenuation of cell death occurred in both differentiated and non-differentiated cells, and could also be induced by other cholesterol oxidation by-products such as 25-hydroxycholesterol and 27-hydroxycholesterol. Moreover, 24-SOHC treatment upregulated the expression of liver X receptor (LXR) target genes, thereby inducing ATP-binding cassette transporter. When LXRβ was knocked down by siRNA, the adaptive response was greatly diminished. Therefore, 24-SOHC represents another example of positive oxidative stress; which works via transcriptional activation of LXR signaling pathway, leading to neuronal protection against further 7KC-triggered cellular toxicity.

Positive effects of protein oxidation products

Cardioprotection by S-nitrosylation of a single cysteine residue on the mitochondrial complex I subunit ND3

Mammalian mitochondrial complex I has at least 45 subunits and many of them are redox-sensitive proteins that can undergo redox modifications by ROS or RNS [82]. Recently, Chouchani et al. reported that *S*-nitrosylation of the ND3 subunit within complex I could protect cardiomyocytes against cell death induced by cardiac ischemia reperfusion injury [30]. As this *S*-nitrosylation occurred on cysteine-39 of ND3 and was induced by a mitochondria-selective *S*-nitrosylating agent (named mitoSNO) administered at the onset of reperfusion, the authors presented an excellent postconditioning paradigm whereby the nitrosylation of a single cysteine residue can trigger a positive oxidative stress condition that protects against cardiac ischemic injury.

S-cysteine sulfenation of the Parkinson's disease-associated protein DJ-1 is neuroprotective

Parkinson's disease (PD) is an age-related neurodegenerative disorder. While it is known that mutations in the gene that encodes DJ-1, a PD-related protein, can abolish neuroprotective function, the underlying mechanisms have been elusive. Madian et al. have recently provided convincing evidence that DJ-1's protective function in PD is due to the conversion of a cysteine's sulfhydryl group (–SH) to an *S*-sulfenation product (–SOH) [32]. The authors further demonstrated that mutations occurring on the DJ-1 gene that disrupted or interfered with this –SH to –SOH conversion on cysteine residue 106 could abolish DJ-1's neuroprotective function. This study thus provides another example of ROS-induced positive oxidative stress in age-related neurodegenerative disease.

Summary

The above representative examples demonstrate that lipid peroxidation by-products and protein oxidation adducts can have tremendous prophylactic effects on aging-related diseases. Fig. 1 shows the relative magnitudes of oxidative stress and the potential corresponding effects. Basically, while a basal level of ROS/RNS and oxidative stress is essential for cell survival [21,22], severe oxidative stress or damage associated with a highly elevated level of ROS/RNS production will inevitably impair the cells' self-repair ability and thus can lead to cell death [22]. Importantly, a moderate level of oxidative stress, i.e., positive oxidative stress, induced by a moderate level of ROS/RNS, can be triggered by a variety of stressors to protect against further lethal challenges that otherwise would cause cell death and tissue injury [22,23,27].

Perspectives

Given that ROS/RNS are short-lived molecules and that the molecular signatures imprinted by these ROS/RNS on lipids and proteins can actually execute the ultimate function of positive oxidative stress, including redox signaling and activation of transcriptional factors [27], further studies will need to be undertaken to identify more targets in a variety of stress settings. Moreover, the underlying mechanisms of such identified targets, especially their prophylactic roles in aging and aging-associated disease tolerance will also need to be elucidated. It is the author's belief that induction of positive oxidative stress could serve as a valuable prophylactic or therapeutic approach targeting aging and aging-associated diseases.

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References

[1] G. Groeger, C. Quiney, T.G. Cotter, Hydrogen peroxide as a cell-survival signaling molecule, Antioxid. Redox Signaling 11 (2009) 2655–2671.
[2] D. Knoefler, M. Thamsen, M. Koniczek, N.J. Niemuth, A.K. Diederich, U. Jakob, Quantitative in vivo redox sensors uncover oxidative stress as an early event in life, Mol. Cell 47 (2012) 767–776.
[3] G. Groeger, F. Doonan, T.G. Cotter, M. Donovan, Reactive oxygen species regulate prosurvival ERK1/2 signaling and bFGF expression in gliosis within the retina, Invest. Ophthalmol. Vis. Sci. 53 (2012) 6645–6654.
[4] E. Bevilacqua, S.Z. Gomes, A.R. Lorenzon, M.S. Hoshida, A.M. Amarante-Paffaro, NADPH oxidase as an important source of reactive oxygen species at the mouse maternal-fetal interface: putative biological roles, Reprod. Biomed. Online 25 (2012) 31–43.
[5] J. Watson, Oxidants, antioxidants and the current incurability of metastatic cancers, Open Biol. 3 (2013) 120144.
[6] M.P. Murphy, How mitochondria produce reactive oxygen species, Biochem. J. 417 (2009) 1–13.
[7] J. St-Pierre, J.A. Buckingham, S.J. Roebuck, M.D. Brand, Topology of superoxide production from different sites in the mitochondrial electron transport chain, J. Biol. Chem. 277 (2002) 44784–44790.
[8] S. Miwa, J. St-Pierre, L. Partridge, M.D. Brand, Superoxide and hydrogen peroxide production by Drosophila mitochondria, Free Radical Biol. Med. 35 (2003) 938–948.
[9] S. Drose, U. Brandt, Molecular mechanisms of superoxide production by the mitochondrial respiratory chain, Adv. Exp. Med. Biol. 748 (2012) 145–169.
[10] L.J. Yan, N. Thangthaeng, N. Sumien, M.J. Forster, Serum dihydrolipoamide dehydrogenase is a labile enzyme, J. Biochem. Pharmacol. Res. 1 (2013) 30–42.
[11] A.A. Starkov, G. Fiskum, C. Chinopoulos, B.J. Lorenzo, S.E. Browne, M.S. Patel, M.F. Beal, Mitochondrial alpha-ketoglutarate dehydrogenase complex generates reactive oxygen species, J. Neurosci. 24 (2004) 7779–7788.
[12] A. Ambrus, L. Tretter, V. Adam-Vizi, Inhibition of the alpha-ketoglutarate dehydrogenase-mediated reactive oxygen species generation by lipoic acid, J. Neurochem. 109 (Suppl 1) (2009) 222–229.
[13] A. Ambrus, B. Torocsik, L. Tretter, O. Ozohanics, V. Adam-Vizi, Stimulation of reactive oxygen species generation by disease-causing mutations of lipoamide dehydrogenase, Hum. Mol. Genet. 20 (2011) 2984–2995.
[14] A. Ambrus, V. Adam-Vizi, Molecular dynamics study of the structural basis of dysfunction and the modulation of reactive oxygen species generation by pathogenic mutants of human dihydrolipoamide dehydrogenase, Arch. Biochem. Biophys. 538 (2013) 145–155.
[15] A. Manea, NADPH oxidase-derived reactive oxygen species: involvement in vascular physiology and pathology, Cell Tissue Res. 342 (2010) 325–339.
[16] J. Bylund, K.L. Brown, C. Movitz, C. Dahlgren, A. Karlsson, Intracellular generation of superoxide by the phagocyte NADPH oxidase: how, where, and what for? Free Radical Biol. Med. 49 (2010) 1834–1845.
[17] R. Harrison, Physiological roles of xanthine oxidoreductase, Drug Metab. Rev. 36 (2004) 363–375.
[18] A. Agarwal, A. Banerjee, U.C. Banerjee, Xanthine oxidoreductase: a journey from purine metabolism to cardiovascular excitation-contraction coupling, Crit. Rev. Biotechnol. 31 (2011) 264–280.
[19] E. Cadenas, K.J. Davies, Mitochondrial free radical generation, oxidative stress, and aging, Free Radical Biol. Med. 29 (2000) 222–230.
[20] L. Mandelker, Introduction to oxidative stress and mitochondrial dysfunction, Vet. Clin. North. Am. Small. Anim. Pract. 38 (2008) 1–30.
[21] Y.M. Janssen-Heininger, B.T. Mossman, N.H. Heintz, H.J. Forman, B. Kalyanaraman, T. Finkel, J.S. Stamler, S.G. Rhee, A. van der Vliet, Redox-based regulation of signal transduction: principles, pitfalls, and promises, Free Radical Biol. Med. 45 (2008) 1–17.
[22] L.A. Sena, N.S. Chandel, Physiological roles of mitochondrial reactive oxygen species, Mol. Cell 48 (2012) 158–167.
[23] N.L. Malinin, X.Z. West, T.V. Byzova, Oxidation as "the stress of life", Aging (Albany NY) 3 (2011) 906–910.
[24] C. Gorrini, I.S. Harris, T.W. Mak, Modulation of oxidative stress as an anticancer strategy, Nat. Rev. Drug Discov. 12 (2013) 931–947.
[25] A.M. Pickering, L. Vojtovich, J. Tower, A.D. KJ, Oxidative stress adaptation with acute, chronic, and repeated stress, Free Radical Biol. Med. 55 (2013) 109–118.
[26] K.J. Davies, Oxidative stress, antioxidant defenses, and damage removal, repair, and replacement systems, IUBMB Life 50 (2000) 279–289.
[27] I. Milisav, B. Poljsak, D. Suput, Adaptive response, evidence of cross-resistance and its potential clinical use, Int. J. Mol. Sci. 13 (2012) 10771–10806.
[28] B.N. Ames, M.K. Shigenaga, Oxidants are a major contributor to aging, Ann. N.Y. Acad. Sci. 663 (1992) 85–96.
[29] Z. Cai, L.J. Yan, Protein oxidative modifications: beneficial roles in disease and health, J. Biochem. Pharmacol. Res. 1 (2013) 15–26.
[30] E.T. Chouchani, C. Methner, S.M. Nadtochiy, A. Logan, V.R. Pell, S. Ding, A. M. James, H.M. Cocheme, J. Reinhold, K.S. Lilley, L. Partridge, I.M. Fearnley, A. J. Robinson, R.C. Hartley, R.A. Smith, T. Krieg, P.S. Brookes, M.P. Murphy, Cardioprotection by *S*-nitrosation of a cysteine switch on mitochondrial complex I, Nat. Med. 19 (2013) 753–759.
[31] L. Asatryan, O. Ziouzenkova, R. Duncan, A. Sevanian, Heme and lipid peroxides in hemoglobin-modified low-density lipoprotein mediate cell survival and adaptation to oxidative stress, Blood 102 (2003) 1732–1739.
[32] A.G. Madian, J. Hindupur, J.D. Hulleman, N. Diaz-Maldonado, V.R. Mishra, E. Guigard, C.M. Kay, J.C. Rochet, F.E. Regnier, Effect of single amino acid substitution on oxidative modifications of the Parkinson′s disease-related protein, DJ-1, Mol. Cell. Proteomics 11 (2012) 010892 (M111).
[33] F. Bosetti, G. Yu, R. Zucchi, S. Ronca-Testoni, G. Solaini, Myocardial ischemic preconditioning and mitochondrial F1F0-ATPase activity, Mol. Cell. Biochem. 215 (2000) 31–37.
[34] T. Mori, H. Muramatsu, T. Matsui, A. McKee, T. Asano, Possible role of the superoxide anion in the development of neuronal tolerance following ischaemic preconditioning in rats, Neuropathol. Appl. Neurobiol. 26 (2000) 31–40.
[35] M. Ristow, S. Schmeisser, Extending life span by increasing oxidative stress, Free Radical Biol. Med. 51 (2011) 327–336.
[36] F. Wiegand, W. Liao, C. Busch, S. Castell, F. Knapp, U. Lindauer, D. Megow, A. Meisel, A. Redetzky, K. Ruscher, G. Trendelenburg, I. Victorov, M. Riepe, H.C. Diener, U. Dirnagl, Respiratory chain inhibition induces tolerance to focal cerebral ischemia, J. Cereb. Blood Flow Metab. 19 (1999) 1229–1237.
[37] A.M. Stowe, T. Altay, A.B. Freie, J.M. Gidday, Repetitive hypoxia extends endogenous neurovascular protection for stroke, Ann. Neurol. 69 (2011) 975–985.
[38] M.R. Bigdeli, Neuroprotection caused by hyperoxia preconditioning in animal stroke models, Sci. World J. 11 (2011) 403–421.
[39] Y. Soejima, Q. Hu, P.R. Krafft, M. Fujii, J. Tang, J.H. Zhang, Hyperbaric oxygen preconditioning attenuates hyperglycemia-enhanced hemorrhagic transformation by inhibiting matrix metalloproteinases in focal cerebral ischemia in rats, Exp. Neurol. 247 (2013) 737–743.
[40] V. Duveau, S. Arthaud, H. Serre, A. Rougier, G. Le Gal La Salle, Transient hyperthermia protects against subsequent seizures and epilepsy-induced cell damage in the rat, Neurobiol. Dis. 19 (2005) 142–149.
[41] M.A. Zieger, M.P. Gupta, Hypothermic preconditioning of endothelial cells attenuates cold-induced injury by a ferritin-dependent process, Free Radical Biol. Med. 46 (2009) 680–691.
[42] M. Blanco, I. Lizasoain, T. Sobrino, J. Vivancos, J. Castillo, Ischemic preconditioning: a novel target for neuroprotective therapy, Cerebrovasc. Dis. 21 (Suppl. 2) (2006) 38–47.
[43] Y. Bhagatte, D. Lodwick, N. Storey, Mitochondrial ROS production and subsequent ERK phosphorylation are necessary for temperature preconditioning of isolated ventricular myocytes, Cell Death Dis. 3 (2012) e345.
[44] T.L. Vanden Hoek, L.B. Becker, Z. Shao, C. Li, P.T. Schumacker, Reactive oxygen species released from mitochondria during brief hypoxia induce preconditioning in cardiomyocytes, J. Biol. Chem. 273 (1998) 18092–18098.
[45] V.M. Costa, R. Silva, R. Ferreira, F. Amado, F. Carvalho, M. de Lourdes Bastos, R.A. Carvalho, M. Carvalho, F. Remiao, Adrenaline in pro-oxidant conditions elicits intracellular survival pathways in isolated rat cardiomyocytes, Toxicology 257 (2009) 70–79.
[46] C. Penna, D. Mancardi, R. Rastaldo, P. Pagliaro, Cardioprotection: a radical view Free radicals in pre and postconditioning, Biochim. Biophys. Acta 1787 (2009) 781–793.
[47] K. Tejima, M. Arai, H. Ikeda, T. Tomiya, M. Yanase, Y. Inoue, K. Nagashima, T. Nishikawa, N. Watanabe, M. Omata, K. Fujiwara, Ischemic preconditioning protects hepatocytes via reactive oxygen species derived from Kupffer cells in rats, Gastroenterology 127 (2004) 1488–1496.
[48] H.T. Facundo, R.S. Carreira, J.G. de Paula, C.C. Santos, R. Ferranti, F.R. Laurindo, A.J. Kowaltowski, Ischemic preconditioning requires increases in reactive oxygen release independent of mitochondrial K^+ channel activity, Free Radical Biol. Med. 40 (2006) 469–479.
[49] J. Kim, H.S. Jang, K.M. Park, Reactive oxygen species generated by renal ischemia and reperfusion trigger protection against subsequent renal ischemia and reperfusion injury in mice, Am. J. Physiol. Renal Physiol. 298 (2010) F158–F166.
[50] M. Ristow, K. Zarse, A. Oberbach, N. Kloting, M. Birringer, M. Kiehntopf, M. Stumvoll, C.R. Kahn, M. Bluher, Antioxidants prevent health-promoting effects of physical exercise in humans, Proc. Nat. Acad. Sci. U.S.A. 106 (2009) 8665–8670.
[51] V. Fernandez, G. Tapia, P. Varela, P. Cornejo, L.A. Videla, Upregulation of liver inducible nitric oxide synthase following thyroid hormone preconditioning: suppression by *N*-acetylcysteine, Biol. Res. 42 (2009) 487–495.
[52] V. Fernandez, G. Tapia, P. Varela, L. Gaete, G. Vera, C. Mora, M.T. Vial, L.A. Videla, Causal role of oxidative stress in liver preconditioning by thyroid hormone in rats, Free Radical Biol. Med. 44 (2008) 1724–1731.
[53] S.C. Correia, R.X. Santos, S.M. Cardoso, M.S. Santos, C.R. Oliveira, P.I. Moreira, Cyanide preconditioning protects brain endothelial and NT2 neuron-like cells against glucotoxicity: role of mitochondrial reactive oxygen species and HIF-1alpha, Neurobiol. Dis. 45 (2012) 206–218.
[54] R. Salie, J.A. Moolman, A. Lochner, The mechanism of beta-adrenergic preconditioning: roles for adenosine and ROS during triggering and mediation, Basic Res. Cardiol. 107 (2012) 281.
[55] C.A. O′Brian, F. Chu, Post-translational disulfide modifications in cell signaling—role of inter-protein, intra-protein, *S*-glutathionyl, and *S*-cysteaminyl

disulfide modifications in signal transmission, Free Radical Res. 39 (2005) 471–480.
[56] P. Ghezzi, V. Bonetto, M. Fratelli, Thiol-disulfide balance: from the concept of oxidative stress to that of redox regulation, Antioxid. Redox Signaling 7 (2005) 964–972.
[57] Y. Shimizu, L.M. Hendershot, Oxidative folding: cellular strategies for dealing with the resultant equimolar production of reactive oxygen species, Antioxid. Redox Signaling 11 (2009) 2317–2331.
[58] Z. Guo, S. Kozlov, M.F. Lavin, M.D. Person, T.T. Paull, ATM activation by oxidative stress, Science 330 (2010) 517–521.
[59] W. Li, J. Zhang, W. An, The conserved CXXC motif of hepatic stimulator substance is essential for its role in mitochondrial protection in H2O2-induced cell apoptosis, FEBS Lett. 584 (2010) 3929–3935.
[60] P.C. Wei, Y.H. Hsieh, M.I. Su, X.J. Jiang, P.H. Hsu, W.T. Lo, J.Y. Weng, Y.M. Jeng, J.M. Wang, P.L. Chen, Y.C. Chang, K.F. Lee, M.D. Tsai, J.Y. Shew, W.H. Lee, Loss of the oxidative stress sensor NPGPx compromises GRP78 chaperone activity and induces systemic disease, Mol. Cell (2012).
[61] C.S. Queiroga, A.S. Almeida, C. Martel, C. Brenner, P.M. Alves, H.L. Vieira, Glutathionylation of adenine nucleotide translocase induced by carbon monoxide prevents mitochondrial membrane permeabilization and apoptosis, J, Biol, Chem. 285 (2010) 17077–17088.
[62] Y. Xiong, J.D. Uys, K.D. Tew, D.M. Townsend, *S*-Glutathionylation: from molecular mechanisms to health outcomes, Antioxid. Redox Signaling 15 (2011) 233–270.
[63] A. Pastore, F. Piemonte, *S*-Glutathionylation signaling in cell biology: progress and prospects, Eur. J. Pharm. Sci. 46 (2012) 279–292.
[64] D. Pimentel, D.J. Haeussler, R. Matsui, J.R. Burgoyne, R.A. Cohen, M.M. Bachschmid, Regulation of cell physiology and pathology by protein *S*-glutathionylation: lessons learned from the cardiovascular system, Antioxid. Redox Signaling 16 (2012) 524–542.
[65] K. Kaiserova, S. Srivastava, J.D. Hoetker, S.O. Awe, X.L. Tang, J. Cai, A. Bhatnagar, Redox activation of aldose reductase in the ischemic heart, J. Biol. Chem. 281 (2006) 15110–15120.
[66] K. Kaiserova, X.L. Tang, S. Srivastava, A. Bhatnagar, Role of nitric oxide in regulating aldose reductase activation in the ischemic heart, J. Biol. Chem. 283 (2008) 9101–9112.
[67] K. Wetzelberger, S.P. Baba, M. Thirunavukkarasu, Y.S. Ho, N. Maulik, O.A. Barski, D.J. Conklin, A. Bhatnagar, Postischemic deactivation of cardiac aldose reductase: role of glutathione *S*-transferase P and glutaredoxin in regeneration of reduced thiols from sulfenic acids, J. Biol. Chem. 285 (2010) 26135–26148.
[68] F. Li, P. Sonveaux, Z.N. Rabbani, S. Liu, B. Yan, Q. Huang, Z. Vujaskovic, M.W. Dewhirst, C.Y. Li, Regulation of HIF-1alpha stability through *S*-nitrosylation, Mol. Cell 26 (2007) 63–74.
[69] L.J. Yan, L. Liu, M.J. Forster, Reversible inactivation of dihydrolipoamide dehydrogenase by Angeli's salt, Acta Biophys. Sin. (Sheng Wu Wu Li Hsueh Bao) 28 (2012) 341–350.
[70] M.W. Foster, D.T. Hess, J.S. Stamler, Protein *S*-nitrosylation in health and disease: a current perspective, Trends Mol. Med. 15 (2009) 391–404.
[71] S.M. Haldar, J.S. Stamler, *S*-nitrosylation: integrator of cardiovascular performance and oxygen delivery, J. Clin. Invest. 123 (2013) 101–110.
[72] C. Jacob, E. Battaglia, T. Burkholz, D. Peng, D. Bagrel, M. Montenarh, Control of oxidative posttranslational cysteine modifications: from intricate chemistry to widespread biological and medical applications, Chem. Res. Toxicol. 25 (2012) 588–604.
[73] A. Pastore, F. Piemonte, Protein glutathionylation in cardiovascular diseases, Int. J. Mol. Sci. 14 (2013) 20845–20876.
[74] Y.M. Go, D.P. Jones, Thiol/disulfide redox states in signaling and sensing, Crit. Rev. Biochem. Mol. Biol. 48 (2013) 173–181.
[75] L.J. Yan, N. Sumien, N. Thangthaeng, M.J. Forster, Reversible inactivation of dihydrolipoamide dehydrogenase by mitochondrial hydrogen peroxide, Free Radical Res. 47 (2013) 123–133.
[76] C.M. Cremers, U. Jakob, Oxidant sensing by reversible disulfide bond formation, J. Biol. Chem. 288 (2013) 26489–26496.
[77] J.P. Brennan, R. Wait, S. Begum, J.R. Bell, M.J. Dunn, P. Eaton, Detection and mapping of widespread intermolecular protein disulfide formation during cardiac oxidative stress using proteomics with diagonal electrophoresis, J. Biol. Chem. 279 (2004) 41352–41360.
[78] N.J. Kettenhofen, M.J. Wood, Formation, reactivity, and detection of protein sulfenic acids, Chem. Res. Toxicol. 23 (2010) 1633–1646.
[79] J. Sun, E. Murphy, Protein *S*-nitrosylation and cardioprotection, Circ. Res. 106 (2010) 285–296.
[80] Y.J. Surh, J.K. Kundu, M.H. Li, H.K. Na, Y.N. Cha, Role of Nrf2-mediated heme oxygenase-1 upregulation in adaptive survival response to nitrosative stress, Arch. Pharm. Res. 32 (2009) 1163–1176.
[81] A. Okabe, Y. Urano, S. Itoh, N. Suda, R. Kotani, Y. Nishimura, Y. Saito, N. Noguchi, Adaptive responses induced by 24S-hydroxycholesterol through liver X receptor pathway reduce 7-ketocholesterol-caused neuronal cell death, Redox Biol. 2 (2014) 28–35.
[82] J. Hirst, Mitochondrial complex I, Annu. Rev. Biochem. 82 (2013) 551–575.
[83] A.M. Brambrink, A. Schneider, H. Noga, A. Astheimer, B. Gotz, I. Korner, A. Heimann, M. Welschof, O. Kempski, Tolerance-Inducing dose of 3-nitropropionic acid modulates bcl-2 and bax balance in the rat brain: a potential mechanism of chemical preconditioning, J. Cereb. Blood Flow Metab. 20 (2000) 1425–1436.
[84] A. Hoshi, T. Nakahara, M. Ogata, T. Yamamoto, The critical threshold of 3-nitropropionic acid-induced ischemic tolerance in the rat, Brain Res. 1050 (2005) 33–39.
[85] P. Klivenyi, A.A. Starkov, N.Y. Calingasan, G. Gardian, S.E. Browne, L. Yang, P. Bubber, G.E. Gibson, M.S. Patel, M.F. Beal, Mice deficient in dihydrolipoamide dehydrogenase show increased vulnerability to MPTP, malonate and 3-nitropropionic acid neurotoxicity, J. Neurochem. 88 (2004) 1352–1360.
[86] A. Carriere, T.G. Ebrahimian, S. Dehez, N. Auge, C. Joffre, M. Andre, S. Arnal, M. Duriez, C. Barreau, E. Arnaud, Y. Fernandez, V. Planat-Benard, B. Levy, L. Penicaud, J.S. Silvestre, L. Casteilla, Preconditioning by mitochondrial reactive oxygen species improves the proangiogenic potential of adipose-derived cells-based therapy, Arterioscler. Thromb. Vasc. Biol. 29 (2009) 1093–1099.
[87] P.J. Hanley, J. Daut, K(ATP) channels and preconditioning: a re-examination of the role of mitochondrial K(ATP) channels and an overview of alternative mechanisms, J. Mol. Cell. Cardiol. 39 (2005) 17–50.
[88] E.J. Kim, Y.G. Yoo, W.K. Yang, Y.S. Lim, T.Y. Na, I.K. Lee, M.O. Lee, Transcriptional activation of HIF-1 by RORalpha and its role in hypoxia signaling, Arterioscler. Thromb. Vasc. Biol. 28 (2008) 1796–1802.
[89] S.M. Jones, A.E. Novak, J.P. Elliott, The role of HIF in cobalt-induced ischemic tolerance, Neuroscience 252 (2013) 420–430.
[90] R.J. McMurtrey, Z. Zuo, Isoflurane preconditioning and postconditioning in rat hippocampal neurons, Brain Res. 1358 (2010) 184–190.
[91] X. Sun, J. Sun, L. Liu, Z. Ding, Isoflurane preconditioning and postconditioning in multiple organ protection, J. Biochem. Pharmacol. Res. 1 (2013) 6–14.
[92] R.Z. Zhan, H. Fujihara, H. Baba, T. Yamakura, K. Shimoji, Ischemic preconditioning is capable of inducing mitochondrial tolerance in the rat brain, Anesthesiology 97 (2002) 896–901.
[93] P. Eaton, R.M. Bell, A.C. Cave, M.J. Shattock, Ischemic preconditioning: a potential role for protein *S*-thiolation? Antioxid. Redox Signaling 7 (2005) 882–888.
[94] D.J. Hausenloy, A.M. Wynne, D.M. Yellon, Ischemic preconditioning targets the reperfusion phase, Basic Res. Cardiol. 102 (2007) 445–452.
[95] A.M. Stowe, B.K. Wacker, P.D. Cravens, J.L. Perfater, M.K. Li, R. Hu, A.B. Freie, O. Stuve, J.M. Gidday, CCL2 upregulation triggers hypoxic preconditioning-induced protection from stroke, J. Neuroinflammation. 9 (2012) 33.
[96] M.R. Schmidt, S.B. Kristiansen, H.E. Botker, Remote ischemic preconditioning: no loss in clinical translation, Circ. Res. 113 (2013) 1278–1280.
[97] S.B. Kristiansen, O. Henning, R.K. Kharbanda, J.E. Nielsen-Kudsk, M.R. Schmidt, A.N. Redington, T.T. Nielsen, H.E. Botker, Remote preconditioning reduces ischemic injury in the explanted heart by a KATP channel-dependent mechanism, Am. J. Physiol. Heart Circ. Physiol. 288 (2005) H1252–H1256.
[98] H. Zhao, C. Ren, X. Chen, J. Shen, From rapid to delayed and remote postconditioning: the evolving concept of ischemic postconditioning in brain ischemia, Curr. Drug Targets 13 (2012) 173–187.
[99] R. Geracitano, A. Tozzi, N. Berretta, F. Florenzano, E. Guatteo, M.T. Viscomi, B. Chiolo, M. Molinari, G. Bernardi, N.B. Mercuri, Protective role of hydrogen peroxide in oxygen-deprived dopaminergic neurones of the rat substantia nigra, J. Physiol. 568 (2005) 97–110.
[100] K.D. Pendergrass, A.V. Boopathy, G. Seshadri, K. Maiellaro-Rafferty, P.L. Che, M.E. Brown, M.E. Davis, Acute preconditioning of cardiac progenitor cells with hydrogen peroxide enhances angiogenic pathways following ischemia-reperfusion injury, Stem Cells Dev. 22 (2013) 2414–2424.
[101] L.A. Ahmed, H.A. Salem, M.N. Mawsouf, A.S. Attia, A.M. Agha, Cardioprotective effects of ozone oxidative preconditioning in an in vivo model of ischemia/reperfusion injury in rats, Scand. J. Clin. Lab. Invest. 72 (2012) 345–354.
[102] H. Chen, B. Xing, X. Liu, B. Zhan, J. Zhou, H. Zhu, Z. Chen, Ozone oxidative preconditioning inhibits inflammation and apoptosis in a rat model of renal ischemia/reperfusion injury, Eur. J. Pharmacol. 581 (2008) 306–314.