ELSEVIER

European Journal of Pharmacology 448 (2002) 225–230

ejp

www.elsevier.com/locate/ejphar

Hydrogen peroxide production by monoamine oxidase during ischemia/reperfusion

Oksana R. Kunduzova, Pascale Bianchi, Angelo Parini*, Claudie Cambon

INSERM U 388, Pharm. Moleculaire et Physiopathologie Renale Institut Louis Bugnard, CHU Rangueil, Bat. L3, 31403 Toulouse Cedex 4, France

Received 7 January 2002; received in revised form 28 May 2002; accepted 31 May 2002

Abstract

Reactive oxygen species have been postulated to play a crucial role in the pathogenesis of renal ischemia-reperfusion injury. However, the intracellular sources of reactive oxygen species during ischemia-reperfusion are still unclear. In the present study, we examined whether catecholamine-degrading enzymes monoamine oxidases contribute to hydrogen peroxide (H_2O_2) generation during ischemia-reperfusion using an in vivo rat model of unilateral renal ischemia. The monoamine oxidases were characterized in homogenates of renal cortex by enzyme assay and by Western blot analysis. The monoamine oxidase-dependent H_2O_2 production was measured by luminol-amplified chemiluminescence assay. Renal monoamine oxidase activity and H_2O_2 generation by monoamine oxidases were suppressed during ischemia. The monoamine oxidase-dependent H_2O_2 production was observed during the first 15 min of reperfusion. In addition, enzyme assays showed that monoamine oxidase is also activated in this period. Rat pre-treatment with the irreversible inhibitor of monoamine oxidase, pargyline, prevented H_2O_2 production. These data suggest that monoamine oxidases are a potential source of H_2O_2 generation in the early reperfusion following ischemia, which could be involved in renal ischemia-reperfusion injury.

Keywords: Ischemia-reperfusion; Monoamine oxidase; Hydrogen peroxide; Kidney; Pargyline

1. Introduction

Renal ischemia-reperfusion injury is a complex phenomenon that involves specific sequences of cellular perturbations and the interaction of multiple pathogenetic mechanisms. Although the exact mechanisms involved in the pathogenesis of renal ischemia-reperfusion injury have not been fully elucidated, it is generally believed that reactive oxygen species are key mediators of the reperfusion-induced damage to the kidney. The excessive formation of reactive oxygen species causes lipid peroxidation of cell membranes (Offord et al., 2000; Sevanian and Ursini, 2000; Waterfall et al., 1995), protein and enzyme oxidation (Eaton et al., 1999; Naskalski and Bartosz, 2000) and some irreversible DNA changes (Burkitt and Duncan, 2000; Elliott et al., 2000; Lopez-Torres et al., 2000) leading to cell death. Support for the chain of events implicating reactive oxygen species in ischemia-reperfusion injury stems from in vitro and in vivo experiments in which administration of scavenging systems or antioxidants attenuated ischemia-reperfusion injury (Cuzzocrea et al., 2001; Galang et al., 2000; Garcia et al., 2000). Much research has been focused on identifying sources of reactive oxygen species and determining whether increased oxidant production is a component of the ischemia-reperfusion injury. Monoamine oxidases, which catalyze the oxidative deamination of biogenic amines such as noradrenaline, tyramine, serotonin and dopamine, are a potential source of reactive oxygen species. Monoamine oxidase exists in two functional isoenzyme forms, monoamine oxidase-A and monoamine oxidase-B, each of which shows preferential affinity for substrates and specificity toward inhibitors (Youdim and Finberg, 1991). It has been recently recognized that monoamine oxidase-A is the predominant enzyme involved in the deamination of endogenous or exogenous amines in rat renal proximal tubule cells (Guimaraes and Soares-da Silva, 1998).

Recent studies suggest that monoamine oxidases contribute to increase in H_2O_2 production (Simonson et al., 1993) and catecholamine release (Damsma et al., 1990; Ishii

* Corresponding author. Tel.: +33-5-61-32-26-22; fax: +33-5-62-17-25-54.

E-mail address: parini@toulouse.inserm.fr (A. Parini).

0014-2999/02/$ - see front matter © 2002 Elsevier Science B.V. All rights reserved.
PII: S0014-2999(02)01913-1

et al., 1993) during brain ischemia and reperfusion. Althought the kidney contains one of the highest monoamine oxidase activity, until now, the involvement of these enzymes in reactive oxygen species generation during renal ischemia-reperfusion is not clear.

To determine whether monoamine oxidase is a potential source of H_2O_2 during renal ischemia-reperfusion, we measured the monoamine oxidase activity and monoamine oxidase-dependent H_2O_2 production during ischemia and in the early and late phases of reperfusion. Our results showed that monoamine oxidases are a potential source of H_2O_2 in the early reperfusion period following ischemia in the rat kidney.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats weighing 140–190 g (Harlan ZI Du Malcourlet, France) were housed individually in standard laboratory cages with ad libitum access to food and water. Rats were anesthetized with sodium pentobarbital (60 mg/kg, intraperitoneally). The jugular vein was cannulated with a polyethylene catheter (PE-10) for the administration of drugs. Ischemia was induced by clamping of the right renal artery for 45 min using a nontraumatic vascular clip. During the operation animals were kept on a surgical thermostatically controlled table at 38 ± 1 °C under anesthesia. The right and left kidneys were removed at the end of the ischemic period (0 h) and after 5 min, 15 min, 30 min, 1 h, 6 h, 24 h, 48 h, 72 h and 168 h of reperfusion. Both postischemic and contralateral kidneys were immediately frozen in liquid nitrogen and stored at − 80 °C until further assay.

2.2. Experimental protocol

The rats were divided into three groups. Saline (group 1) or pargyline (group 2) at the dose of 6 mg/kg was administered intravenously 15 min prior to ischemia. All drugs were administered in a volume of 100 μl/100 g of body weight. Sham-operated animals (group 3) were subjected to the same surgical procedure without clamping the right renal artery.

2.3. Western blot

Homogenate extracts were solubilized in loading buffer (60 mM Tris–HCl, pH 6.8, containing 2% SDS, 10% glycerol, 1% β-mercaptoethanol and 0.05% bromophenol blue) at 100 °C for 5 min and subjected to 10% SDS-polyacrylamide gel electrophoresis. Proteins (30 μg) were transferred to polyvinylidene difluoride membranes with a semidry electroblotter (Transblot, Biorad) for 1 h at 450 mA. The blots were saturated with 5% nonfat dried milk for monoamine oxidase immunoblot overnight at 4 °C. Then, blots were washed twice, and incubated for 1 h at room temperature with a rabbit polyclonal antisera to monoamine oxidase-A and monoamine oxidase-B (Gargalidis-Moudanos et al., 1997). After washing, membranes were incubated with peroxidase labeled anti-rabbit for 40 min, bands were detected using the ECL reaction.

2.4. Monoamine oxidase activity

The monoamine oxidase-A activity was measured from renal cortex homogenates by a modification of method of Yu (1986) using [^{14}C]serotonin as substrate. Just prior to analysis frozen renal cortex was homogenized in 50 mM phosphate buffer, pH 7.4 (NaH_2PO_4 0.2 M, Na_2HPO_4 0.2 M, phenylmethylsulfonylfluoride 0.1 mM, Bacitracine 10 μg/ml, Soybean trypsin inhibitor 2 μg/ml) with a Potter homogenizer (Bioblock Scientific, Illkirch, France). The sonicated samples containing approximately 50-μg protein were incubated at 37 °C for 10 min in a final volume of 50 μl in the same buffer in the presence of [^{14}C]serotonin (300 μM). Pargyline (10^{-5} M) was used to define specific monoamine oxidase activity. The reaction was terminated by the addition of 100 μl HCl, 4 N at 4 °C. The acid oxidation products were extracted with the addition of 1 ml toluene–ethylacetate (1:1, v/v) and the radioactivity contained in the organic phase was analysed by liquid scintillation spectrometry at 97% efficiency.

2.5. Assay of H_2O_2 production

H_2O_2 production was measured in the nonsonicated renal cortex homogenates by chemiluminescence in the presence of luminol (30 μM) and peroxidase (0.1 U/ml) using a thermostatically (37 °C) controlled luminometer (Bio-Orbit 1251), as described previously (Pizzinat et al., 1999). The generation of chemiluminescence triggered with 10 μM of tyramine, was continuously monitored for 60 min, and the area under the curve was analysed by the Bio-Orbit Multi-Use program. To determine if selective and nonselective inhibitors of monoamine oxidases affect H_2O_2 formation, the renal cortex homogenates were preincubated for 20 min prior to tyramine addition at 37 °C with 1 μM clorgyline (to inhibit monoamine oxidase-A activity) and 1 μM lazabemide (to inhibit monoamine oxidase-B activity).

2.6. Quantification of proteins

Protein concentration was determined with the Bio-rad DC protein assay reagents (Bio-rad Lab), with γ globulins as the standard.

2.7. Statistical analysis

The data were analyzed and presented as means ± S.E.M. Statistical analyses were performed using analysis of var-

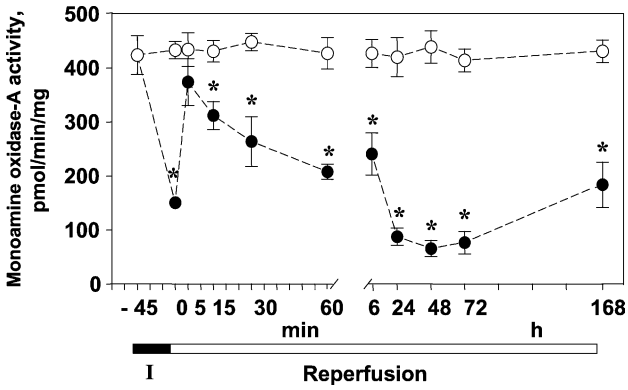

Fig. 1. Time course of changes in monoamine oxidase activity in control and ischemic kidneys during ischemia (I) and reperfusion. The monoamine oxidase-A activity was measured using [^{14}C]serotonin as substrate in renal cortex homogenates from control (-○-) and ischemic (-●-) kidneys. Data represent means ± S.E.M. of six experiments. * $P < 0.001$ compared with control kidney.

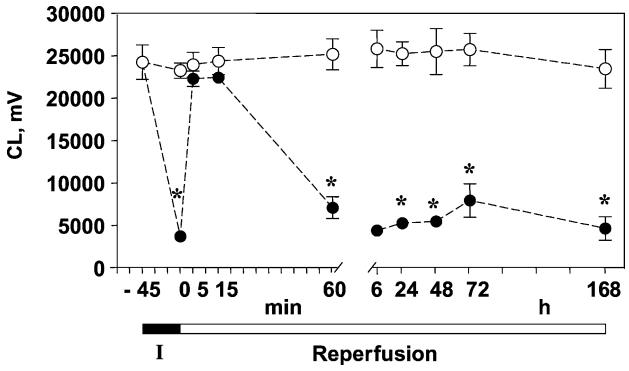

Fig. 3. Time course of changes in monoamine oxidase-dependent H_2O_2 production in control and ischemic kidneys during ischemia (I) and reperfusion. (B) The total chemiluminescence (CL) emission (area under the curve) was monitored for 60 min after tyramine (10 μM) addition in renal cortex homogenates from control (-○-) and ischemic (-●-) kidneys. Data represent means ± S.E.M. of six experiments. * $P < 0.001$ compared with control kidney.

iance (ANOVA) followed by Mann–Whitney U test. Differences were considered significant at $P < 0.05$.

2.8. Materials

[^{14}C]serotonin: 5-hydroxytryptamine binoxalatate (52.3 mCi/mmol) was purchased from NEN™ Life Science Products (Boston, MA, USA); Bio-rad DC protein assay reagents were obtained from Bio-rad Laboratories (Hercules, CA, USA). Clorgyline hydrochloride was purchased from Research Biochemicals International (MA, USA). Lazabemide was provided by F. Hoffmann La Roche (Basel, Switzerland). Pargyline hydrochloride and all other chemicals were purchased from Sigma (Paris, France).

3. Results

In order to assess whether monoamine oxidase activity is changed during ischemia-reperfusion, we characterized monoamine oxidase by enzyme assay using [^{14}C]serotonin as substrate for monoamine oxidase-A in homogenates of ischemic-reperfused and control sham-operated kidneys. As shown in Fig. 1, renal ischemia caused a marked decrease in monoamine oxidase-A activity (66 ± 2% vs. control), whereas reperfusion during the first 5 min resulted in a rapid increase in enzyme activity reaching values similar to those observed in control kidneys. However, this full recovery of monoamine oxidase-A activity in the early phase of reperfusion was transient and gradually decreased during the first 24 h. A strong inhibition of monoamine oxidase-A activity was still observed 3 days upon reperfusion (Fig. 1). In addition, monoamine oxidases were also identified and characterized by Western blot analysis using an antiserum obtained from rabbit immunized with a peptide common to both monoamine oxidase-A and -B (Gargalidis-Moudanos et al., 1997). As shown in Fig. 2, Western blot analysis performed in renal cortex from control sham-operated rats and rats subjected to ischemia followed by 15 min of reperfusion revealed two

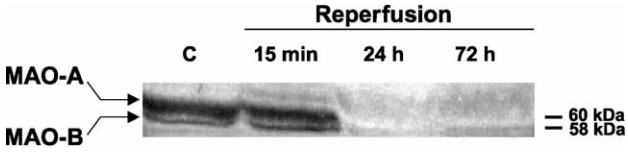

Fig. 2. Effect of ischemia-reperfusion on renal monoamine oxidase-A and monoamine oxidase-B expression. Kidneys from control sham-operated rats (C) and ischemic kidneys were removed after 15 min, 24 h and 72 h of reperfusion. The monoamine oxidase-A (MAO-A) and monoamine oxidase-B (MAO-B) expression were revealed in homogenates from renal cortex (30 μg of proteins) by Western blot analysis using an anti-monoamine oxidase-A/B antiserum. The blots are representative of the results obtained from four animals.

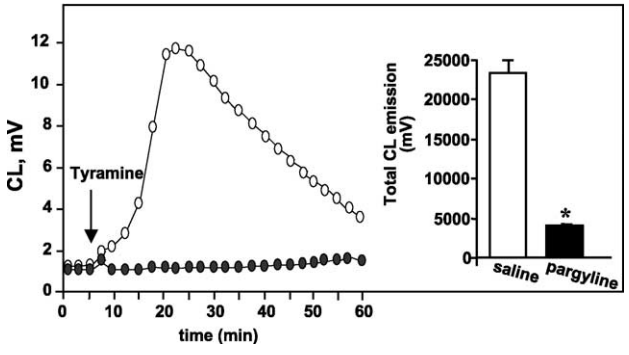

Fig. 4. Effect of pargyline pre-treatment on monoamine oxidase-dependent H_2O_2 after 15 min of reperfusion following unilateral ischemia. Representative traces (of six experiments) of the generation of chemiluminescence (CL) after 10 μM tyramine addition in renal cortex homogenates from rats pre-treated with saline (-○-) or 6 mg/kg (i.v.) pargyline (-●-) 15 min before ischemia (45 min). Histograms show the total CL emission (area under the curve) monitored for 60 min and expressed as means ± S.E.M. of values from six independent experiments. * $P < 0.001$ compared with saline-treated rats.

proteins with the apparent molecular weight expected for monoamine oxidase-A and -B (~ 60 and 58 kDa, respectively). After 15 min of reperfusion, the immunoreactivity of the bands corresponding to monoamine oxidase-A and -B was similar to that found in control kidneys. In contrast, monoamine oxidase-A and -B bands were undetectable after 24 and 72 h of reperfusion (Fig. 2).

Hydrogen peroxide generation by monoamine oxidases after ischemia-reperfusion was determined by a chemiluminescence-based assay using the monoamine oxidase-A/B substrate tyramine. We have previously shown that this technique allows to evaluate the relative contribution of each monoamine oxidase isoenzyme to the H_2O_2 production (Pizzinat et al., 1999). The results presented in Fig. 3 show that the profile of monoamine oxidase-dependent H_2O_2 generation measured in renal cortex homogenates from ischemic-reperfused and control sham-operated groups of rats was similar to that found for monoamine oxidase-A activity. Indeed, H_2O_2 produced during tyramine degradation was (i) decreased by $84 \pm 0.3\%$ after ischemia alone, (ii) recovered to the control levels after 5–15 min of reperfusion and (iii) returned to the ischemic level at 6 h after reperfusion. The decrease in H_2O_2 generation was maintained up to 7 days after reperfusion.

In order to determine whether the transient recovery of monoamine oxidase activity and monoamine oxidase-dependent H_2O_2 production in the early phase of reperfusion could be prevented, we treated rats with the irreversible monoamine oxidase-A/B inhibitor, pargyline. As shown in Fig. 4, rat pre-treatment with a single dose of pargyline (6 mg/kg, i.v.) significantly decreased monoamine oxidase-A activity and H_2O_2-generated chemiluminescence by $86 \pm 2\%$ and $81 \pm 1\%$, respectively, after 5 min of reperfusion.

In addition, to specify the isoenzymes responsible for H_2O_2 production, renal cortex from rats after 5 min of reperfusion following ischemia was pre-incubated with monoamine oxidase-A (clorgyline) or monoamine oxidase-B (lazabemide) inhibitors for 20 min before tyramine addition. As shown in Fig. 5, H_2O_2 production was strongly inhibited by the monoamine oxidase-A inhibitor and to a less extent by the monoamine oxidase-B inhibitor. These data suggest the predominant role of monoamine oxidase-A in H_2O_2 production after reperfusion.

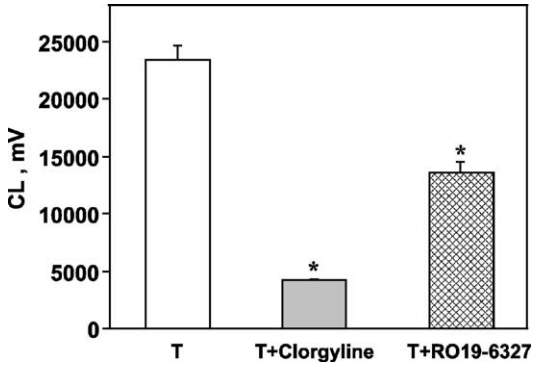

Fig. 5. Effect of monoamine oxidase-A and monoamine oxidase-B inhibitors on tyramine-induced H_2O_2 production after 5 min of reperfusion following unilateral ischemia. The total chemiluminescence (CL) emission (area under the curve) was measured for 60 min after 10 μM tyramine (T) addition in renal cortex homogenates in the absence and presence of monoamine oxidase-A (clorgyline, 1 μM) or monoamine oxidase-B (lazabemide, 1 μM) inhibitor. Data represent means ± S.E.M. of three experiments. * $P < 0.01$ compared with value in the absence of inhibitors.

4. Discussion

This study examines the role of monoamine oxidases as a possible source of H_2O_2 produced in rat kidney after ischemia-reperfusion. Our results demonstrate that monoamine oxidase-A activity dramatically changes in response to the different phases of ischemia-reperfusion in rat kidney. In addition, we also provide evidence that monoamine oxidase inhibition by pargyline pre-treatment prevented the monoamine oxidase-dependent H_2O_2 production in the early reperfusion period.

In the present study, we show for the first time the expression of monoamine oxidases at the different time points after ischemia-reperfusion. Our data provide evidence for a strong inhibition of renal monoamine oxidase activity and monoamine oxidase-dependent H_2O_2 generation during ischemic period. Similar observations have been also reported in an in vivo model of brain ischemia where monoamine oxidase activity was dramatically reduced during ischemia (Goroshinskaia et al., 1989; Ishii et al., 1993). A loss of enzymatic activity in this period could led to the accumulation of catecholamines, which may modulate the final responses of cells to the ischemic injury. There is considerable evidence that ischemia is accompanied by a massive release of neurotransmitters such as dopamine, noradrenaline and serotonin (Baker et al., 1991; Obrenovitch and Richards, 1995).

One of the most relevant result of our study is the demonstration that monoamine oxidases are a potential source of H_2O_2 generation in the early reperfusion period (5–15 min), whereas prolonged reperfusion induced a strong suppression of monoamine oxidase-dependent H_2O_2 production and monoamine oxidase activity. Western blot analysis showed that the recovery of the enzyme activity and H_2O_2 generation in the early phase of reperfusion were not due to a change in the amount of monoamine oxidase-A protein. Therefore, it is conceivable that the restoration of the enzyme activity is related to conformational changes of monoamine oxidase-A. In contrast, the loss of monoamine oxidase-A activity after prolonged reperfusion may related to a modification of protein synthesis or degradation as shown by the disappearance of the monoamine oxidase immunoreactive bands.

The post-reperfusion H_2O_2 production fully prevented by pargyline treatment suggests that pharmacological treatment with monoamine oxidase inhibitors could be a potential

approach to decrease the H_2O_2-mediated tissue injury. To determine whether monoamine oxidase-A and/or monoamine oxidase-B affect ischemia-induced H_2O_2 production after reperfusion, we evaluated monoamine oxidase-dependent H_2O_2 production in the presence of selective monoamine oxidase inhibitors by chemiluminescence assay. Our study demonstrates that monoamine oxidase-A predominantly contributes to H_2O_2 generation during early reperfusion. The evidence for the importance of these enzymes as a significant source of H_2O_2 in an in vivo model of brain ischemia has been also provided by Simonson et al. (1993), who demonstrated that monoamine oxidase inhibitors block increased H_2O_2 production observed during the first 5 min of reperfusion. The excessive formation of free radicals in the early phase of reperfusion following ischemia has been documented in a number of organs including kidney (Hower et al., 1996; Kadkhodaee et al., 1996; Pincemail et al., 1993), brain (Lancelot et al., 1995; Li et al., 1999; Simonson et al., 1993), heart (Premaratne et al., 1994; Ravingerova et al., 1999) and skeletal muscle (Schlag et al., 1999). It is possible that the enhanced generation of reactive oxygen species during early reperfusion, leading to membrane lipid peroxidation, may initiate cascade of events that ultimately contribute to cell death and tissue damage. This view agrees with results obtained in the rat kidney, where increased lipid peroxidation was shown as measured by the enhanced levels of malondialdehyde after 5–10 min of reperfusion (Akcetin et al., 2000). Furthermore, it has recently been recognized that oxidative stress induced by ischemia-reperfusion activates in the early reperfusion period certain members of the mitogen-activated protein kinase (MAPK) cascade including extracellular signal–regulated kinases (ERKs), c-Jun NH_2-terminal protein kinases (JNKs) or stress-activated protein kinases (SAPKs), and p38 MAPKs (Pombo et al., 1994; Wei et al., 2001; Fryer et al., 2001; Wu et al., 2000). Altogether, these different observations clearly demonstrate that the critical reactive oxygen species-mediated injury occurs in the early reperfusion period.

After transient recovery of enzymatic activity and monoamine oxidase-dependent H_2O_2 production in the early reperfusion period (5–15 min), we have observed a significant reduction in monoamine oxidase activity within 3 days and, to a less degree, 7 days after reperfusion, indicating either overall depression of mitochondrial metabolism or dysfunction of mitochondrial enzyme systems. Similarly, Ishii et al. (1993) demonstrated the suppression of monoamine oxidase activity after reperfusion in brain model of ischemia in gerbils. Futhermore, Ishii et al. were able to demonstrate the changes in catecholamine metabolism during reperfusion caused by monoamine oxidase inhibition and a consequent shift toward catechol-*O*-methyltransferase metabolism and possibly other catabolic routes. The changes occurring in monoamine metabolism after reperfusion are of interest because they may play a critical role in the progression of ischemia-reperfusion injury. It has been suggested that inhibition of monoamine oxidase could represent a protective action from ischemia-reperfusion injury in the kidney (Troncoso et al., 1995). However, mechanisms by which monoamine oxidase prevents complications associated with ischemia-induced changes in renal function are largely unknown.

In summary, we have demonstrated for the first time that monoamine oxidases are a potential source of H_2O_2 generation in the early reperfusion period following ischemia in the rat kidney. If the monoamine oxidase-mediated increase in production of H_2O_2 is indeed involved in the generation of renal ischemia-reperfusion damage, then the pre-treatment with monoamine oxidase inhibitors might have potential clinical relevance. Currently, efforts are under way to further investigate the possible protective effect of pargyline and the mechanisms involved in the renal ischemia-reperfusion injury.

Acknowledgements

This work was supported by the Institut National de la Santé et de la Recherche Médicale and the Région Midi-Pyrénées (France).

References

Akcetin, Z., Pregla, R., Busch, A., Kessler, G., Heynemann, H., Holtz, J., Bromme, H., 2000. Lipid peroxidation and the expressional regulation of the heat-shock response during ischemia-reperfusion of rat kidney. Urol. Int. 65, 32–39.

Baker, A.J., Zornow, M.H., Scheller, M.S., Yaksh, T.L., Skilling, S.R., Smullin, D.H., Larson, A.A., Kuczenski, R., 1991. Changes in extracellular concentrations of glutamate, aspartate, glycine, dopamine, serotonin, and dopamine metabolites after transient global ischemia in the rabbit brain. J. Neurochem. 57, 1370–1379.

Burkitt, M.J., Duncan, J., 2000. Effects of trans-resveratrol on copper-dependent hydroxyl-radical formation and DNA damage: evidence for hydroxyl-radical scavenging and a novel, glutathione-sparing mechanism of action. Arch. Biochem. Biophys. 381, 253–263.

Cuzzocrea, S., Riley, D.P., Caputi, A.P., Salvemini, D., 2001. Antioxidant therapy: a new pharmacological approach in shock, inflammation, and ischemia/reperfusion injury. Pharmacol. Rev. 53, 135–159.

Damsma, G., Boisvert, D.P., Mudrick, L.A., Wenkstern, D., Fibiger, H.C., 1990. Effects of transient forebrain ischemia and pargyline on extracellular concentrations of dopamine, serotonin, and their metabolites in the rat striatum as determined by in vivo microdialysis. J. Neurochem. 54, 801–808.

Eaton, P., Li, J.M., Hearse, D.J., Shattock, M.J., 1999. Formation of 4-hydroxy-2-nonenal-modified proteins in ischemic rat heart. Am. J. Physiol., Heart Circ. Physiol. 276, H935–H943.

Elliott, R.M., Astley, S.B., Southon, S., Archer, D.B., 2000. Measurement of cellular repair activities for oxidative DNA damage. Free Radic. Biol. Med. 28, 1438–1446.

Fryer, R.M., Patel, H.H., Hsu, A.K., Gross, G.J., 2001. Stress-activated protein kinase phosphorylation during cardioprotection in the ischemic myocardium. Am. J. Physiol., Heart Circ. Physiol. 281, H1184–H1192.

Galang, N., Sasaki, H., Maulik, N., 2000. Apoptotic cell death during ischemia/reperfusion and its attenuation by antioxidant therapy. Toxicology 148, 111–118.

Garcia, J.J., Martinez-Ballarin, E., Robinson, M., Allue, J.L., Reiter, R.J., Osuna, C., Acuna-Castroviejo, D., 2000. Protective effect of beta-carbo-

lines and other antioxidants on lipid peroxidation due to hydrogen peroxide in rat brain homogenates. Neurosci. Lett. 294, 1–4.

Gargalidis-Moudanos, C., Remaury, A., Pizzinat, N., Parini, A., 1997. Predominant expression of monoamine oxidase B isoform in rabbit renal proximal tubule: regulation by I_2 imidazoline ligands in intact cells. Mol. Pharmacol. 51, 637–643.

Goroshinskaia, I.A., Stoianovich, T., Michich, D.V., Mrshulia, B.B., 1989. Properties of monoamine oxidase in the brain of mongolian gerbils during cerebral ischemia. Vopr. Med. Khim. 35, 112–115.

Guimaraes, J.T., Soares-da Silva, P., 1998. The activity of MAO A and B in rat renal cells and tubules. Life Sci. 62, 727–737.

Hower, R., Minor, T., Schneeberger, H., Theodorakis, J., Rembold, S., Illner, W.D., Hofmann, G.O., Fraunberger, P., Isselhard, W., Land, W., 1996. Assessment of oxygen radicals during kidney transplantation—effect of radical scavenger. Transpl. Int. 9 (Suppl. 1), S479–S482.

Ishii, H., Stanimirovic, D.B., Chang, C.J., Mrsulja, B.B., Spatz, M., 1993. Dopamine metabolism and free-radical related mitochondrial injury during transient brain ischemia in gerbils. Neurochem. Res. 18, 1193–1201.

Kadkhodaee, M., Hanson, G.R., Towner, R.A., Endre, Z.H., 1996. Detection of hydroxyl and carbon-centred radicals by EPR spectroscopy after is chaemia and reperfusion of the rat kidney. Free Radic. Res. 25, 31–42.

Lancelot, E., Callebert, J., Revaud, M.L., Boulu, R.G., Plotkine, M., 1995. Detection of hydroxyl radicals in rat striatum during transient focal cerebral ischemia: possible implication in tissue damage. Neurosci. Lett. 197, 85–88.

Li, P.A., Liu, G.J., He, Q.P., Floyd, R.A., Siesjo, B.K., 1999. Production of hydroxyl free radical by brain tissues in hyperglycemic rats subjected to transient forebrain ischemia. Free Radic. Biol. Med. 27, 1033–1040.

Lopez-Torres, M., Romero, M., Barja, G., 2000. Effect of thyroid hormones on mitochondrial oxygen free radical production and DNA oxidative damage in the rat heart. Mol. Cell. Endocrinol. 168, 127–134.

Naskalski, J.W., Bartosz, G., 2000. Oxidative modifications of protein structures. Adv. Clin. Chem. 35, 161–253.

Obrenovitch, T.P., Richards, D.A., 1995. Extracellular neurotransmitter changes in cerebral ischaemia. Cerebrovasc. Brain Metab. Rev. 7, 1–54.

Offord, E., Van Poppel, G., Tyrrell, R., 2000. Markers of oxidative damage and antioxidant protection: current status and relevance to disease. Free Radic. Res. 33, S5–S19.

Pincemail, J., Defraigne, J.O., Franssen, C., Bonnet, P., Deby-Dupont, G., Pirenne, J., Deby, C., Lamy, M., Limet, M., Meurisse, M., 1993. Evidence for free radical formation during human kidney transplantation. Free Radic. Biol. Med. 15, 343–348.

Pizzinat, N., Copin, N., Vindis, C., Parini, A., Cambon, C., 1999. Reactive oxygen species production by monoamine oxidases in intact cells. Naunyn-Schmiedeberg's Arch. Pharmacol. 359, 428–431.

Pombo, C.M., Bonventre, J.V., Avruch, J., Woodgett, J.R., Kyriakis, J.M., Force, T., 1994. The stress-activated protein kinases are major c-Jun amino-terminal kinases activated by ischemia and reperfusion. J. Biol. Chem. 269, 26546–26551.

Premaratne, S., Suehiro, A., Suehiro, G.T., Arakaki, H.Y., McNamara, J.J., 1994. Detection of hydroxyl free radicals in the reperfused primate heart. Free Radic. Res. 21, 19–25.

Ravingerova, T., Slezak, J., Tribulova, N., Dzurba, A., Uhrik, B., Ziegelhoffer, A., 1999. Free oxygen radicals contribute to high incidence of reperfusion-induced arrhythmias in isolated rat heart. Life Sci. 65, 1927–1930.

Schlag, M.G., Clarke, S., Carson, M.W., Harris, K.A., Potter, R.F., 1999. The effect of mannitol versus dimethyl thiourea at attenuating ischemia/reperfusion-induced injury to skeletal muscle. J. Vasc. Surg. 29, 511–521.

Sevanian, A., Ursini, F., 2000. Lipid peroxidation in membranes and low-density lipoproteins: similarities and differences. Free Radic. Biol. Med. 29, 306–311.

Simonson, S.G., Zhang, J., Canada, A.T., Su, Y.F., Benveniste, H., Piantadosi, C.A., 1993. Hydrogen peroxide production by monoamine oxidase during ischemia-reperfusion in the rat brain. J. Cereb. Blood Flow Metab. 13, 125–134.

Troncoso, P., Dominguez, J., Martinez, L., Zambrano, N., 1995. Oxidative damage markers in a renal ischemic-reperfusion model: the protective effect of monoamine oxidase inhibition. Transplant. Proc. 27, 1836–1838.

Waterfall, A.H., Singh, G., Fry, J.R., Marsden, C.A., 1995. Detection of the lipid peroxidation product malonaldehyde in rat brain in vivo. Neurosci. Lett. 200, 69–72.

Wei, S., Rothstein, E.C., Fliegel, L., Dell'Italia, L.J., Lucchesi, P.A., 2001. Differential MAP kinase activation and Na(+)/H(+) exchanger phosphorylation by H(2)O(2) in rat cardiac myocytes. Am. J. Physiol. Cell Physiol. 281, C1542–C1550.

Wu, D.C., Ye, W., Che, X.M., Yang, G.Y., 2000. Activation of mitogen-activated protein kinases after permanent cerebral artery occlusion in mouse brain. J. Cereb. Blood Flow Metab. 20, 1320–1330.

Youdim, M.B., Finberg, J.P., 1991. New directions in monoamine oxidase A and B selective inhibitors and substrates. Biochem. Pharmacol. 41, 155–162.

Yu, P.H., 1986. Monoamine oxidase. In: Boulton, A.A., Baker, G.B., Yu, P.H. (Eds.), Neuromethods, Neurotransmitters, Enzymes. Humana Press, Clifton, pp. 235–272.