Recent advances in liver preconditioning: Thyroid hormone, n-3 long-chain polyunsaturated fatty acids and iron

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Abstract

Liver preconditioning (PC), defined as an enhanced tolerance to injuring stimuli induced by previous specific maneuvers triggering beneficial functional and molecular changes, is of crucial importance in human liver transplantation and major hepatic resection. For these reasons, numerous PC strategies have been evaluated in experimental models of ischemia-reperfusion liver injury, which have not been transferred to clinical application due to side effects, toxicity and difficulties in implementation, with the exception of the controversial ischemic PC. In recent years, our group has undertaken the assessment of alternate experimental liver PC protocols that might have application in the clinical setting. These include thyroid hormone ($T_3$), n-3 long-chain polyunsaturated fatty acids (n-3 LCPUFA), or iron, which suppressed liver damage due to the 1 h ischemia-20 h reperfusion protocol. $T_3$, n-3 LCPUFA and iron are hormetic agents that trigger biologically beneficial effects in the low-dose range, whose multifactorial mechanisms of action are discussed in the work.

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INTRODUCTION

Liver functioning is characterized by a multiplicity of processes that include most of the pathways for intermediary metabolism, biotransformation of xenobiotics, plasma protein biosynthesis, excretion and secretion of various types of molecules. With the exception of hyperglycemic conditions, the high energy requirements to support liver functions are primarily met by fatty acid oxidation, making the liver highly dependent on O$_2$ supply and susceptible to hypoxic or anoxic conditions. Liver damage underlying cellular death is associated with cholestasis, viral hepatitis, drug-induced injury, obesity$^{[1]}$, and ischemia-reperfusion (IR) episodes, including liver transplantation, hepatic resection, low-blood pressure conditions and abdominal surgery requiring hepatic vascular occlusion$^{[2-5]}$. IR injury is a phenomenon in which cellular damage due to hypoxia is exacerbated following restoration of O$_2$ and nutrient supply$^{[2-5]}$. In these situations, different types of ischemia can occur in the liver: namely, (1) warm ischemia inducing hepatocyte and sinusoidal endothelial cell (SEC) death, a feature of hepatic trauma, hypovolemic shock and inflow occlusion during...
In general terms, organ preconditioning (PC) is defined as an increased tolerance to IR injury afforded by previous specific maneuvers triggering beneficial functional and molecular changes, a phenomenon initially described by Murry et al[3] in the heart. PC strategies evaluated in experimental models of IR liver injury include: (1) pharmacological approaches targeting tumor necrosis factor-α (TNF-α) response, mitochondrial dysfunction, reactive oxygen species (ROS) production, microcirculatory disorders or neutrophil infiltration; (2) gene therapy directed to up-regulation of proteins abrogating ROS production, apoptosis and nuclear factor-κB (NF-κB) activation or down-regulating of intercellular adhesion molecule-1 and P-selectin expression reducing neutrophil recruitment; and (3) surgical strategies such as ischemic preconditioning (IP) or other strategies underlying moderate oxidative stress development (for specific references see[4-8,10]). The latter group of PC maneuvers includes development of hyperthermia[11], hyperbaric oxygen therapy[12] or the administration of the model oxidants tert-butyl hydroperoxide[13], doxorubicin[14] and ozone[15]. However, due to toxicity, side effects and difficulties in implementation, these experimental PC strategies have not been transferred to clinical application, with the exception of IP[8,14]. Although IP proved to be useful in human liver resections[17-19] and in human liver transplantation[20,21], this PC maneuver remains controversial[22-25]. For these reasons, our group has recently undertaken the evaluation of alternate experimental liver PC strategies that might have application in the clinical setting; namely, administration of thyroid hormone (L-3,3,5-triiodothyronine, T₃)[26], n-3 long-chain polyunsaturated fatty acids (n-3 LCPUFA)[27] or iron[28], prior to an IR protocol.

**THYROID HORMONE LIVER PRECONDITIONING**

Liver PC by in vivo T₃ administration is based on the calorigenic action of thyroid hormones leading to stimulation and maintenance of basal thermogenesis[20], a response that is carried out through genomic and nongenomic signaling mechanisms[1,13]. In the liver, this effect is evidenced by enhancement in the rate of O₂ consumption, with consequent increment in ROS generation[11,13] by mechanisms primarily triggered in hepatocytes and in Kupffer cells (Figure 1). ROS produced in Kupffer cells activate redox-sensitive transcription factors such as NF-κB, signal transducer and activator of transcription 3 (STAT3) or activating protein 1 (AP-1), as shown by suppression of T₃-induced DNA binding of these proteins by in vitro pretreatment with the antioxidants α-tocopherol and N-acetylcysteine or the Kupffer cell inactivator gadolinium chloride[14,15]. Under these conditions, activation of NF-κB and AP-1 in Kupffer cells is associated with up-regulation of the expression of genes for the cytokines TNFα, interleukin (IL)-1 and IL-6[16,17], with enhanced synthesis and release into hepatic sinusoids (Figure 1). Interaction of Kupffer cell-derived TNF-α with TNF receptor 1 may trigger two responses in hepatocytes[18]: namely, (1) NF-κB activation via inhibitor of κB kinase (IKK) phosphorylation leading to the expression of antioxidant (manganese superoxide dismutase, inducible nitric oxide synthase), anti-apoptotic (Bcl2) and type I acute-phase (haptoglobin) proteins[39,40]; and (2) AP-1 activation via c-Jun N-terminal kinase (NK) phosphorylation leading to up-regulation of hepatocyte proliferation[41] (Figure 1). In addition, interaction of Kupffer cell-derived IL-6 with IL-6 receptor through its binding to the gp130 receptor subunit[42] may activate Janus kinase (JAK)/STAT3 system and the transcription of both type I (haptoglobin) and type II (β-fibrinogen) acute-phase protein genes[43] (Figure 1). Activation of NF-κB, STAT3 and AP-1 by Kupffer cell-derived TNF-α and IL-6 may be reinforced by ROS generated within hepatocytes by different enzymatic mechanisms triggered by T₃ (Figure 1). These cytoprotective responses could be contributed by additional processes triggered by T₃ administration: including (1) post-transcriptional up-regulation of the acute-phase protein ferritin through increased iron-induced displacement of iron regulatory protein from the iron-responsive element in ferritin mRNA[40]; and (2) transcriptional up-regulation of uncoupling proteins via the classical genomic pathway[39], which have been proposed to decrease the pro-oxidant potential of the liver[36,41].

Recently, in vivo T₃ administration to rats was shown to activate hepatic nuclear factor erythroid 2-related factor 2 (Nrf2), as evidenced by the increased cytosol-to-nuclear translocation observed[41]. Liver Nrf2 activation induced by T₃ appears to be a redox-dependent process due to its abolishment by N-acetylcysteine pretreatment, which may be contributed by Nrf2 phosphorylation related to p38 activation[41]. This would represent a novel and alternate cytoprotective mechanism of T₃ action against free-radical and electrophile toxicity, in addition to that afforded by NF-κB, STAT3 and AP-1 up-regulation[14-36] (Figure 1), considering that Nrf2 controls the expression of antioxidant components, detoxification enzymes or membrane transporters (Figure 1) and interplays with NF-κB affording anti-inflammatory responses[42].

Redox activation of NF-κB, STAT3, AP-1 and Nrf2 up-regulating transcription of protective genes represents an additional non-genomic mechanism of T₃ action to those reported for different cellular processes[43], which is dependent upon the genomic pathway enhancing energy metabolism with ROS production. These observations
Dietary fatty acids, especially LCPUFA, are essential for a nutritional model of non-alcoholic steatosis in rats, with complete regression of fat accumulation in association with higher oxidative stress status and potentiation of humoral immune response; and (2) JNK/STAT3 activation by T3 in a nutritional model of non-alcoholic steatosis in rats, with complete regression of fat accumulation.

n-3 LONG-CHAIN-POLYUNSATURATED FATTY ACID LIVER PRECONDITIONING

Dietary fatty acids, especially LCPUFA, are essential for growth and development in mammals including man,
both n-6 and n-3 LCPUFAs being important as structural components of cellular lipids and substrates for the synthesis of physiological mediators. Among the n-6 series of LCPUFAs, eicosapentaenoic acid (C20:5n-3; EPA) and docosahexaenoic acid (C22:6n-3; DHA), produced from α-linolenic acid (C18:3n-3), have been associated with multiple positive health effects and proposed for the prevention of non transmissible chronic diseases or against heart and liver IR injury. It is considered that attainment of a given n-6/n-3 ratio is crucial for prevention and treatment of several diseases, as a potential sensor for the activation of mechanisms involved in inflammatory processes such as liver IR injury.

Recently, liver PC against IR injury was reported in rats subjected to fish oil (70 mg/kg EPA plus 180 mg/kg DHA) or saline (controls) administration for 7 d, prior to the 1 h ischemia-20 h reperfusion protocol. In vivo n-3 LCPUFA supplementation significantly enhanced liver n-3 LCPUFA content and decreased n-6/n-3 LCPUFA ratios, with prevention of IR-induced liver injury, suppression of oxidative stress, recovery of pro-inflammatory cytokine homeostasis, and NF-κB functionality lost during IR. Several molecular mechanisms can be invoked to explain liver PC by n-3 LCPUFA, including antioxidant and anti-inflammatory responses.

Considering the high susceptibility of n-3 LCPUFAs to free-radical attack with further decomposition, these fatty acids readily undergo in vitro non-enzymatic lipid peroxidation with formation of cyclopentenone-containing J-ring isoprostanes (J-isoprostanes). Gao et al. reported that J-isoprostanes from EPA and DHA oxidation react with sulfhydryl groups in recombinant Keap1, a Cul-containing E3 ubiquitin ligase (Cul3)-Ring box 1 complex responsible for Nrf2 ubiquitination and degradation. This interaction alters Keap1 structure, leading to loss of binding to Cul3, Nrf2 stabilization and nuclear translocation, with expression of the antioxidant enzymes heme-oxygenase-1 and glutamate cysteine ligase, as assessed in cultured HepG2 cells (Figure 2). In agreement with these findings, in vitro EPA supplementation in mice was shown to up-regulate the expression of other Nrf2-dependent antioxidant proteins, namely, glutathione peroxidase, glutathione reductase, glutathione-S-transferase and catalase, with significant increases in liver glutathione content and diminution in lipid peroxidation rate.

Both EPA and DHA have been reported as effective anti-inflammatory and tissue protective mediators, effects that may underlie different mechanisms of action (Figure 2). These include various aspects of eicosanoid metabolism generating n-3 LCPUFA-derived mediators produced in the resolution phase following acute inflam-

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**Figure 2** n-3 long-chain polyunsaturated fatty acid-induced liver preconditioning is associated with antioxidant and anti-inflammatory responses triggered by oxidative products and peroxisome proliferator-activated receptor-α activation. n-3 LCPUFA: n-3 long-chain polyunsaturated fatty acid; COX-2: Cyclooxygenase 2; Keap1: Kelch-like ECH-associated protein 1; S-LOX: S-epoxygenase; NF-κB: Nuclear factor-xB; Nrf2: Nuclear factor-erythroid 2 related factor 2; PPAR-α: Peroxisome proliferator-activated receptor-α.
EPA and DHA can be metabolized by cyclooxygenase-2 (COX-2) and 5-lypoxigenase (5-LOX) to generate E-series and D-series of resolvins in vitro and in vivo, respectively (Figure 2), which exhibit anti-inflammatory effects compared with those derived from arachidonic acid[57]. DHA can also be metabolized by 5-LOX to produce protectins, protecitn D1 being the most potent anti-inflammatory isomer[58] (Figure 2). Resolvins E1, E2 and protectin D1 exert their anti-inflammatory action mainly through inhibition of neutrophil infiltration in target tissues[57,59]. In the case of resolving E1, its binding to G-protein-coupled receptors chemokine-like receptor-1 and leukotriene B4 receptor attenuates the pro-inflammatory effects of NF-κB and leukotriene B4 signaling, respectively[60]. Although the influence of resolvins and protectins has not been evaluated in IR liver injury, mouse kidney subjected to bilateral IR leads to endogenous mobilization and higher blood levels of DHA, with enhanced production of D-series of resolvins and protectins[60]. Moreover, pretreatment with exogenous resolvins was able to protect from IR kidney injury[61]. Interestingly, in vitro DHA supplementation is protective against liver necroinflammatory injury in mice subjected to carbon tetrachloride intoxication, a condition enhancing hepatic formation of the DHA-derived metabolites 17S-hydroxy-DHA (17S-HDHA) and protectin D1[62]. These findings and the protective effect of DHA and 17S-HDHA against in vitro hydrogen peroxide toxicity in hepatocytes establish a significant protective role of n-3 LCPUFA supplementation in well-known animal models of liver injury, which amplifies formation of DHA-derived anti-inflammatory lipid mediators in the liver[63] (Figure 2). In addition to EPA and DHA metabolism by the COX2/5-LOX pathway, these fatty acids may undergo oxygenation by cytochrome P450 NADPH-dependent epoxygenases (Figure 2), with production of multiple epoxyeicosaquateroic acid and epoxydocosapentaenoic acid regioisomers, respectively[57,58], which might have anti-inflammatory effects[63]. The finding that IR elicited a net decrease in the content of n-3 LCPUFA in the liver of EPA plus DHA supplemented rats over that in non-supplemented animals[59], support the contention that in vitro n-3 LCPUFA protection may be related to utilization of the fatty acids in lipid peroxidation, COX-2/5-LOX and cytochrome P450-dependent epoxygenation pathways. However, n-3 LCPUFA β-oxidation and replacement for n-6 LCPUFA in membrane phospholipids cannot be discarded.

In addition to the above discussed mechanisms related to the anti-inflammatory responses of n-3 LCPUFA involving oxidative processes, EPA and DHA may directly alter intracellular signaling pathways associated with transcription factors peroxisome proliferator-activated receptors (PPAR)-α/PPAR-γ and NF-κB/AP-1. The mechanism is based on the findings that LCPUFA, fatty acid derivatives and eicosanoids act as natural ligands for PPARs leading to their activation[64], which physically interact with both the p65 component of NF-κB and the c-Jun component of AP-1 (Figure 2), thus interfering with NF-κB and AP-1 transactivation of inflammatory genes[65]. Alternate mechanisms triggered by PPAR-α activation include: (1) enhancement of 15κB-α and protein expression and its nuclear abundance, with diminution in NF-κB DNA binding activity[65]; (2) decreased 15κB-α degradation, probably due to diminished phosphorylation[56]; and (3) up-regulation of antioxidant enzymes[56,68] (Figure 2) with reduction of the oxidative stress status, leading to loss of NF-κB activation and inflammatory cytokine production[66]. n-3 LCPUFA-induced re-establishment of inflammatory cytokine homeostasis under IR conditions[57,69] is accompanied by improvement of hepatic microcirculation, as a contributory factor protecting the liver against IR injury[67,68]. Although the relevance of n-3 LCPUFA supplementation in conditions underlying IR liver injury in humans has not been evaluated, several clinical studies have reported that supplementation with fish oil, seal oil or purified n-3 LCPUFA reduces hepatic lipid content in obese non-alcoholic fatty liver disease patients[62-66], exhibiting substantial depletion of n-3 LCPUFA content[70]. In addition, n-3 LCPUFA administration improved circulating liver function markers[73], serum triacylglycerol (TAG)[74,75] and tumor necrosis factor-α[76] levels, and hepatic microcirculatory function[77].

**IRON LIVER PRECONDITIONING**

Iron is an essential micronutrient and bio-catalyst of oxidation-reduction reactions that are related to its chemistry promoting electron exchange under aerobic conditions, being crucial for mitochondrial oxidative phosphorylation and other processes requiring enzymes/proteins with iron as a cofactor[78,79]. At the different cell compartments, iron is bound to low-molecular-weight molecules, giving a steady-state concentration of labile iron within the cell. This labile iron pool corresponds to a low-molecular-weight pool of weakly chelated iron that readily passes through the cell, representing a minor fraction of total cellular iron (3%-5%)[79]. The cellular labile iron pool is in equilibrium with (1) iron taken from the diet, delivered into bloodstream, and incorporated into cells through transferring-receptors; (2) iron export; (3) iron reversibly incorporated into heme and non-heme proteins; and (4) iron stored in ferritin, which constitutes a major and safe fraction of the iron that entered into the cell (Figure 3)[79].

The intracellular labile iron pool has been associated with physiological, pharmacological and toxico-logical iron functions. Iron is able to catalyze the conversion of by-products of respiration [superoxide radical (O2•−) and hydrogen peroxide (H2O2)] into hydroxyl radical (HO•) via the Fenton reaction or the Fe2+-assisted Haber-Weiss reaction (Figure 3)[79], thus enhancing the oxidative stress status of the cell. Rats subjected to a sub-chronic iron administration protocol (six doses of 50 mg iron-dextran/kg, ip every second day during 10 d) showed significant enhancement in total iron and in the labile iron pool of...
the liver, with consequent up-regulation of ferritin content, thus establishing a transient oxidative stress condition without development of hepatotoxicity. Under these conditions, a significant protection was afforded by iron administration against liver IR injury, as evidenced by diminution in serum transaminase levels and normal liver architecture observed in iron supplemented animals subjected to IR compared to non-supplemented rats. Iron liver preconditioning against IR could be due to cellular iron metabolism over the 72 h time-period between in vivo iron administration and the settlement of IR in vitro, with consequent ferritin up-regulation sequestering large amounts of administered iron to avoid liver injury, and expansion of the labile iron pool increasing the oxidative stress status that limits the further pro-oxidant challenge of IR. In addition, suppression of the TNF-α response and reversion of the changes in signal transduction and gene expression induced by IR were achieved by in vivo iron administration, with recovery of NF-κB activation and NF-κB-related expression of haptoglobin lost during IR (Figure 3). Haptoglobin is an anti-inflammatory and antioxidant acute-phase protein participating in the acute-phase response of the liver, a reaction restoring homeostasis by contributing to defensive and adaptive capabilities.

From the mechanistic viewpoint, development of transient oxidative stress in the liver of iron supplemented animals may be related to stimulation of different processes in Kupffer cells and hepatocytes. In vivo iron overload alters the functional status of Kupffer cells by increasing the respiratory burst activity without modifying phagocytosis, an effect that is probably related to O$_2$ Equivalents used by NADPH oxidase to produce O$_2^{−}$ and H$_2$O$_2$, which may be further subjected to Fenton/Haber-Weiss reactions (Figure 3). Promotion of biomolecules oxidation and activation of nitric oxide synthase may also contribute to this effect of iron. Iron-induced respiratory burst of Kupffer cells with enhanced ROS production may have a role in NF-κB signaling, as shown by the activation of IKK and NF-κB DNA binding, leading to enhanced TNF-α promoter activity and TNF-α release from cultured Kupffer cells (Figure 3). As proposed for T cells liver preconditioning (Figure 1), TNF-α released from Kupffer cells may trigger protective signaling cascades in hepatocytes, thus achieving protection against IR liver injury. Interestingly, ferritin heavy chain and other protective proteins up-regulation against IR liver injury. Interestingly, ferritin heavy chain and other protective proteins up-regulation against IR liver injury.
chain was identified as an essential mediator of the anti-
oxidant and protective actions of NF-κB, as assessed in
cultured NIN-3T3 cells. This protein is induced down-
stream of NF-κB, providing a transcriptional regulatory
mechanism for ferritin induction through iron-mediated
ROS generation (90) (Figure 3), which represents a potential
approach for anti-inflammatory therapy (91). Up-regulation
of ferritin expression by iron is also under post-transcrip-
tional regulation, a mechanism involving the interaction
of iron regulatory proteins with the iron-responsive ele-
ments in ferritin mRNA, to enhance ferritin synthesis
and concentrate excess iron (84-86), avoiding cytotoxicity
(Figure 3). Besides, iron overload up-regulates hepcidin
expression, an acute-phase protein produced by hepatocy-
tes that controls the dietary absorption, storage and tis-

sue distribution of iron, which exhibits a significant cor-
relation with serum ferritin levels (87). The mechanism of
hepcidin action involves internalization and degradation
of ferropotin, a hepcidin-receptor and iron channel, that
diminishes intestinal iron absorption, iron mobilization
from hepatocytes, and iron recycling by macrophages,
leading to iron entrapment in ferritin at enterocyte, mac-
rophage and hepatocyte level (87). Although regulation of
liver hepcidin transcription by iron involving the bone
morphogenetic protein (BMP) pathway is not completely
understood (87), IL-6/STAT3 signaling is a key effector of
hepcidin expression during inflammatory conditions (88),
a redox-sensitive pathway controlling the expression of
several other acute-phase proteins (Figure 3). In addition
to NF-κB and STAT3, liver Nrf2 signaling may also con-
tribute to iron-induced preconditioning, considering (1)
the enhancement in the expression of liver Nrf2 protein
and catalase, glutathione-S-transferase and heme-oxyge-
nase-1 mRNA in mice subjected to iron overloading (88);
and (2) the significant diminution in hepatic glutathione
levels and in glutamate cysteine ligase activity observed in
Nrf2 (87) mice treated with ferric nitrilotriacetate over wild-
type animals (90) (Figure 3).

CONCLUDING REMARKS

T₃, n-3 LCPUFA and iron can be considered as hormetic
agents (91), which are defined as compounds inducing a
dose-response phenomenon characterized by biologi-
cally beneficial effects in the low-concentration (dose)
range (organ preconditioning) (92-98) and harmful responses
at high concentrations (doses) or after prolonged ex-
posure (thyrotoxicosis (99), gastrointestinal upset/increase
bleeding time (90) and hemochromatosis (99), respectively).
Organ preconditioning by these hormetic agents is not
restricted to the liver (92-98), considering that (1) thyroid
hormone-induced preconditioning against IR injury is
also observed in the heart (100), with a pattern of protec-
tion comparable to that of ischemic preconditioning (97);
(2) beneficial effects of n-3 LCPUFA have been dem-
onstrated in rheumatoid arthritis, inflammatory bowel
disease, coronary artery disease, asthma and sepsis, con-
ditions with inflammation as a key component of their
pathology (100), in addition to neuroinflammation in all
major central nervous system diseases (100); and (3) protec-
tive effects of iron are reported in cardiomyocytes and
heart (99-101), oligodendroglia cells (100) and neurons (100).
T₃, n-3 LCPUFAs or iron liver preconditioning are suitable
for use in the clinical setting, considering that these hormetins are known to be well tolerated in the
treatment of hypothyroidism (101), non-alcoholic fatty liver
disease (72-76) and other diseases (86, 102), respectively.
Interestingly, there is evidence to conclude that n-3
LCPUFAs potentiate the effects of certain drugs, thereby
allowing a reduction of their required dose, thus avoid-
ing adverse effects (86). In agreement with this view, com-
bined n-3 LCPUFA (300 mg/kg for 3 consecutive days)
and T₃ (0.05 mg/kg) administration prevented rat liver
IR injury, whereas separate protocols lack protection (100),
when compared with the preconditioning action afforded by
separate n-3 LCPUFA (300 mg/kg for 7 consecutive
days) (27) or T₃ (0.1 mg/kg) (26). Data discussed in this article
warrants further experimental and clinical research in the
future, to support the incorporation of T₃, n-3 LCPUFA
and iron preconditioning strategies or their combinations
in human liver resections and in human liver transplan-
tation using reduced-size grafts from living donors.

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REFERENCES

1. Videla LA. Oxidative stress signaling underlying liver dis-
ease and hepatoprotective mechanisms. World J Hepatol 2009;
1: 72-78
2. Teoh NC, Farrell GC. Hepatic ischemia reperfusion injury:
pathogenic mechanisms and basis for hepatoprotection. J Gastroen-
terol Hepatol 2005; 18: 891-902
3. Jaeschke H. Molecular mechanisms of hepatic ischemia-
reperfusion injury and preconditioning. Am J Physiol Gastro-
intestinal Liver Physiol 2003; 284: G15-G26
4. Selzner N, Rudiger H, Graf R, Clavien PA. Protective stra-
eggies against ischemic injury of the liver. Gastroenterology
2003; 125: 917-936
5. Banga NR, Homer-Vanniasinkam S, Graham A, Al-Mukhtar
A, White SA, Prasad KR. Ischaemic preconditioning in trans-
plantation and major resection of the liver. Br J Surg 2005;
92: 528-538
6. de Rougemont O, Lehmann K, Clavien PA. Precondition-
ing, organ preservation, and postconditioning to prevent
ischemia-reperfusion injury to the liver. Liver Transpl 2009;
15: 1172-1182
7. Casillas-Ramírez A, Mosbah IB, Ramalho F, Roselló-Catafau
J, Peralta C. Past and future approaches to ischemia-reper-
fusion lesion associated with liver transplantation. Life Sci
2006; 79: 1881-1894
8. Das M, Das DK. Molecular mechanism of preconditioning.
ILJMB Life 2008; 60: 199-203
9. Murry CE, Jennings RB, Reimer KA. Preconditioning with
ischemia: a delay of lethal cell injury in ischemic myocar-
Bahde B, Spiegel HU. Hepatic ischemia-reperfusion injury from bench to bedside. Br J Surg 2010; 97: 1461-1475

Terajima H, Enders G, Thiaener A, Hammer C, Kondo T, Thieric J, Yamamoto Y, Yamaka Y, Messmer K. Impact of hyperthermic preconditioning on postischemic hepatic microcirculatory disturbances in an isolated perfusion model of the rat liver. Hepatology 2000; 31: 407-415

Yu SY, Chiu JH, Yang SD, Yu HY, Hsieh CC, Chen PJ, Lui WY, Wu CW. Preconditioned hyperbaric oxygen protects the liver against ischemia-reperfusion injury in rats. J Surg Res 2005; 128: 28-36

Rüdiger HA, Graf R, Clavien PA. Sub-lethal oxidative stress triggers the protective effects of ischemic preconditioning in the mouse liver. J Hepatol 2003; 39: 972-977 [PMID: 14642614 DOI: 10.1016/S0168-8278(03)00415-X]

Ito K, Ozasa H, Sanada K, Horikawa S. Doxorubicin preconditioning: a protection against rat hepatic ischemia-reperfusion injury. Hepatology 2000; 31: 416-419

Ajamiieh HH, Menendez S, Martinez-Sanchez G, Candelario-Jalil E, Re L, Giuliani A, Fernandez OS. Effects of ozone oxidative preconditioning on nitric oxide generation and cellular redox balance in a rat model of hepatic ischaemia-reperfusion. Liver Int 2004; 24: 55-62

Románque P, Díaz A, Tapia G, Uribe-Echevarria S, Videla LA, Fernandez V. Delayed ischemic preconditioning protects against liver ischemia-reperfusion injury in vivo. Transplant Proc 2010; 42: 1569-1575

Clavien PA, Selzner M, Rüdiger HA, Graf R, Kadyr Z, Rousson V, Jochum W. A prospective randomized study in 100 consecutive patients undergoing major liver resection with versus without ischemic preconditioning. Ann Surg 2003; 238: 843-850; discussion 851-852

Smyrniotis V, Theodoraki K, Arkadopoulos N, Fragulis G, Condi-Pafiti A, Plemenou-Fragou M, Vorsos D, Vassiliou J, Dimakakos P. Ischemic preconditioning versus intermittent vascular occlusion in liver resections performed under selective vascular exclusion: a prospective randomized study. Am J Surg 2006; 192: 669-674

Heizmann O, Lanni A, Chiu JH, Yang SD, Yu HY, Hsieh CC, Chen PJ, Lui WY, Wu CW. Preconditioned hyperbaric oxygenation protects the liver against ischemia-reperfusion injury in rats. J Surg Res 2005; 128: 28-36

Adamo A, Grande L, Marti J, Deulofeu R, Miquel R, Sola A, Rodriguez-Laiz G, Ferrer J, Condi-Pafiti A, Plemenou-Fragou M, Voros D, Vassiliou J, Dimakakos P. Ischemic preconditioning versus intermittent vascular occlusion in liver resections performed under selective vascular exclusion: a prospective randomized study. Am J Surg 2006; 192: 669-674

Bailarini NN, Wente MN, Schemmer P, Diener MK, Hoffmann K, Motschall E, Schmidt J, Weitz J, Büchler MW. Systematic review and meta-analysis of the effect of portal triad clamping on outcome after hepatic resection. Br J Surg 2008; 95: 424-432

Fernández V, Castillo I, Tapia G, Romanque P, Uribe-Echevarria S, Uribe M, Cartier-Ugarté D, Santander G, Vial MT, Videla LA. Thyroid hormone preconditioning: protection against ischemia-reperfusion liver injury in the rat. Hepatology 2007; 45: 170-177

Zúñiga J, Venegas F, Villarreal M, Núñez D, Chandra M, Valenzuela R, Tapia G, Varela P, Videla LA, Fernández V. Protection against in vivo liver ischemia-reperfusion injury by n-3 long-chain polyunsaturated fatty acids in the rat. Free Radic Res 2010; 44: 854-863

Galleano M, Tapia G, Puntarulo S, Varela P, Videla LA, Fernandez V. Liver preconditioning induced by iron in a rat model of ischemia/reperfusion. Life Sci 2011; 89: 221-228

Schwartz HL, Oppenheimer JH. Physiologic and biochemical actions of thyroid hormone. Pharmacol Ther 1978; 3: 349-376

Fernández V, Videla LA. Kupffer cell-dependent signaling in thyroid hormone calorigenesis: possible applications for liver preconditioning. Curr Signal Transf Ther 2009; 4: 144-151

Fernández V, Videla LA. Influence of hyperthyroidism on superoxide radical and hydrogen peroxide production by rat liver submicrovesicular particles. Free Radic Res Commun 1993; 18: 329-335

Venditti P, De Rosa R, De Meo S. Effect of thyroid state on H2O2 production by rat liver mitochondria. Mol Cell Endocrinol 2005; 203: 185-192

Tsukamoto H, Lin M. The role of Kupffer cells in liver injury. In: Wisse E, Knoop DL, Balabaud C, editors. Cells of the Hepatic Sinusoid. Leiden, The Netherlands: Kupffer Cell Foundation, 2008: 244-250

Fernández V, Tapia G, Varela P, Castillo I, Mora C, Moya F, Orellana M, Videla LA. Redox up-regulated expression of rat liver manganese superoxide dismutase and Bcl-2 by thyroid hormone is associated with inhibitor of kappal-alpha phosphorylation and nuclear factor-kappaB activation. J Endocrinol 2005; 186: 539-547

Pappas P, Fernández V, Pino C, Ardtiles R, Videla L. The acute-phase response of the liver in relation to thyroid hormone-induced redox signaling. Free Radic Biol Med 2006; 40: 1628-1635

Fernández V, Reyes S, Bravo S, Sepulveda R, Romanque P, Santander G, Castillo I, Varela P, Tapia G, Videla LA. Involvement of Kupffer cell-dependent signaling in T-induced hepatocyte proliferation in vivo. Biol Chem 2007; 388: 831-837

Hirano T, Ishihara K, Hibi M. Roles of STAT3 in mediating the cell growth, differentiation and survival signals relayed through the IL-6 family of cytokine receptors. Oncogene 2000; 19: 2548-2556

Leedman PJ, Stein AR, Chinn WW, Rogers JT. Thyroid hormone modulates the interaction between iron regulatory proteins and the ferritin mRNA iron-responsive element. J Biol Chem 1996; 271: 12017-12023

Lanni A, Moreno M, Lombardi A, Goglia F. Thyroid hormone and uncoupling proteins. FEBS Lett 2003; 543: 5-10

Goglia F, Skulachev VP. A function for novel uncoupling proteins: antioxidant defense of mitochondrial matrix by translocating fatty acid peroxides from the inner to the outer membrane leaflet. FEBS J 2003; 17: 1585-1591

Románque P, Cornejo P, Valdes S, Videla LA. Thyroid hormone administration induces rat liver Nrf2 activation: suppression by N-acetylcysteine pretreatment. Thyroid 2011; 21: 655-662

Singh S, Vrishi S, Singh BK, Rahman I, Kakkar P. Nrf2-ARE stress response mechanism: a control point in oxidative stress-mediated dysfunctions and chronic inflammatory diseases. Free Radic Res 2010; 44: 1267-1288
43 Davis PJ, Leonard JL, Davis FB. Mechanisms of nongenomic actions of thyroid hormone. Front Neuroendocrinol 2008; 29: 211-218
44 Colambano A, Shinozuka H. Liver regeneration versus direct hyperplasia. FASEB J 1996; 10: 1118-1128
45 Vinayagomoorthi R, Koner BC, Kavitha S, Nandakumar DN, Padma Priya P, Goswami K. Potentiation of humoral immune response and activation of NF-kappaB pathway in lymphocytes in experimentally induced hyperthyroid rats. Cell Immunol 2005; 238: 56-60
46 Nandakumar DN, Koner BC, Vinayagomoorthi R, Nanda N, Negi VS, Goswami K, Bobby Z, Hamide A. Activation of NF-kappaB in lymphocytes and increase in serum immunoglobulin in hyperthyroidism: possible role of oxidative stress. Immunobiology 2008; 213: 409-415
47 Perera A, Simbula G, Simbula M, Pipiri M, Kowalik MA, Sulas P, Cocco MT, Ledda-Columbo GM, Columbo A. Thyroid hormone (T3) and TRbeta agonist GC-1 inhibit/ reverse nonalcoholic fatty liver in rats. FASEB J 2008; 22: 2981-2989
48 Fetterman JW, Zdanowicz MM. Therapeutic potential of n-3 polyunsaturated fatty acids in disease. An J Health Syst Pharm 2009; 66: 1169-1179
49 Ferguson LR, Smith BG, James BJ. Combining nutrition, hypolipidemic drugs, polyunsaturated fatty acids, and eicosanoids are ligands for peroxisome proliferator-activated receptors alpha and delta. Proc Natl Acad Sci USA 1997; 94: 4312-4317
50 Delerive P, De Bosscher K, Besnard S, Vanden Berghe W, Peters JM, Gonzalez FJ, Frucht JC, Tedgui A, Haegeman G, Staels B. Peroxisome proliferator-activated receptor alpha negatively regulates the vascular inflammatory gene response by negative cross-talk with transcription factors NF-κB and AP-1. J Biol Chem 1999; 274: 32048-32054
51 Delerive P, Gervois P, Frucht JC, Staels B. Induction of IkappaBalpha expression as a mechanism contributing to the anti-inflammatory activities of peroxisome proliferator-activated receptor-alpha activators. J Biol Chem 2000; 275: 36703-36707
52 Calder PC. Polyunsaturated fatty acids and inflammation. Prostaglandins Leukot Essent Fatty Acids 2006; 75: 197-202
53 Poynter ME, Daynes RA. Peroxoxome proliferator-activated receptor alpha activation modulates cellular redox status, represses nuclear factor-kappaB signaling, and reduces inflammatory cytokine production in aging. J Biol Chem 1998; 273: 32833-32841
54 Wasawski K, Kume M, Kudo K, Uchimani H, Kikuchi I, Nakagawa Y, Yoshioka M, Yamamoto Y. Changes in the fatty acid composition of the liver with the administration of N-3 polyunsaturated fatty acids and the effects on warm ischemia/reperfusion injury in the rat liver. Shock 2010; 33: 306-314
55 Zhong Z, Thurman RG. A fish oil diet minimizes hepatic reperfusion injury in the low-flow, reflow liver perfusion model. Hepatology 1995; 22: 929-935
56 El-Badry AM, Moritz W, Contaldo C, Tian Y, Graf R, Cla- vien PA. Prevention of reperfusion injury and microcircula
tory failure in macrosteatotic mouse liver by omega-3 fatty acids. J Lipids 2007; 282: 2529-2537
57 Capani M, Calella F, Biagini MR, Genise S, Raimondi L, Bedogni G, Svegliati-Baroni G, Sofi F, Milani S, Abbate R, Surrenti C, Casini A. Prolonged n-3 polyunsaturated fatty acid supplementation ameliorates hepatic steatosis in patients with non-alcoholic fatty liver disease: a pilot study. Aliment Pharmacol Ther 2006; 23: 1143-1151
58 Spadaro L, Magliocco O, Spampinato D, Piro S, Oliveri C, Alagona G, Papa G, Rahuazzo AM, Purrello F. Effects of n-3 polyunsaturated fatty acids on serum adiponectin in patients with non-alcoholic fatty liver disease: a pilot study. Aliment Pharmacol Ther 2006; 23: 1143-1151
59 Zhu FS, Liu S, Chen XM, Huang ZG, Zhang DW. Effects of n-3 polyunsaturated fatty acids from seal oils on nonalcoholic fatty liver disease. Dig Liver Dis 2008; 40: 194-199
60 Hatzitolios A, Savopoulos C, Lazaraki G, Sidiropoulos I, Haritanti P, Lefkopoulou A, Karagiannopoulos G, Tzioufa V, Dimitrios K. Efficacy of omega-3 fatty acids, atorvastatin and orlistat in non-alcoholic fatty liver disease with dyslipidemia. Indian J Gastroenterol 2004; 23: 131-134
61 Tanaka N, Sano K, Horiuichi A, Tanaka E, Kiyosawa K, Aoyama T. Highly purified eicosapentaenoic acid treatment improves non alcoholic steatohepatitis. J Clin Gastroenterol 2008; 42: 413-418
62 Araya J, Rodrigo R, Videla LA, Thiememann L, Orellana M, Gómez-González-Pérez A, Planagumá A, Gronert K, Miquel R, López-Parra M, Titos E, Horrillo R, Ferré N, Deulofeu R, Arroyo V, Rodés J, Clariá J. Docosahexaenoic acid (DHA) blunts liver injury by conversion to protective lipid mediators: protectin D1 and 17S-hydroxy-DHA. FASEB J 2006; 20: 2537-2539
63 Ye D, Zhang D, Oltman C, Dellsperger K, Lee HC, Van-Rollins M. Cytochrome P-450 epoxygenase metabolites of docosahexaenoate potently dilate coronary arterioles by activating large-conductance calcium-activated potassium channels. J Pharmacol Exp Ther 2002; 303: 768-776
64 Forman BM, Chen J, Evans RM. Hypolipidemic drugs, polyunsaturated fatty acids, and eicosanoids are ligands for peroxisome proliferator-activated receptors alpha and delta. Proc Natl Acad Sci USA 1997; 94: 365-390
65 Rodrigo R, Cereceda M, Castillo R, Asenjo R, Zamorano J, Araya J, Castillo-Koch R, Espinoza J, Larraín E. Prevention of atrial fibrillation following cardiac surgery: basis for a novel therapeutic strategy based on non-hypoxic myocardial preconditioning. Pharmacol Ther 2008; 118: 104-127
66 Simopoulos AP. The importance of the omega-6/omega-3 fatty acid ratio in cardiovascular disease and other chronic diseases. Exp Biol Med (Maywood) 2008; 233: 674-688
67 Sevanian A, Hochstein P. Mechanisms and consequences of lipid peroxidation in biological systems. Ann Rev Nutr 1985; 5: 365-390
68 Gao L, Wang J, Sekhar KR, Yin H, Yared NF, Schneider SN, Sasi S, Dalton TP, Anderson ME, Chan JY, Morrow JD, Free- man ML. Novel n-3 fatty acid oxidation products activate Nrf2 by destabilizing the association between Keap1 and Cullulin. J Biol Chem 2007; 282: 45065-45076
69 Zhang DD. Mechanistic studies of the Nrf2-Keap1 signaling pathway. Drug Metab Rev 2006; 38: 769-789
70 Demonz A, Willumsen N, Berge RK. Eicosapentaenoic acid at hypotriglyceridemic dose enhances the hepatic antioxidant defense in mice. Lipids 1992; 27: 968-971
71 de Roos B, Mamrromattis Y, Brouwer IA. Long-chain n-3 polyunsaturated fatty acids: new insights into mechanisms relating to inflammation and coronary heart disease. Br J Pharmacol 2009; 158: 413-428
72 Hong S, Gronert K, Devchand PR, Moussignac RL, Serhan CN. Docosahexaenoic acid and orlistat in non-alcoholic fatty liver disease. FASEB J 2002; 16: 2537-2539
73 Anaya J, Rodrigo R, Videla LA, Thiememann L, Orellana M, Cernea T, Rosalski A, Purrello F, Andrade R, Castellanos A, Serhan CN, Leask A. eicosapentaenoic acid in murine brain, human blood, and glial cells. Autocoids in anti-inflammation. J Biol Chem 2003; 278: 14677-14687
74 Serhan CN, Chiang N, Van Dyke TE. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. Nat Rev Immunol 2008; 8: 349-361
75 Arita M, Ohira T, Sun YP, Elangovan S, Chiang N, Serhan CN. Resolvin E1 selectively interacts with leukotriene B4 receptor BLT1 and ChemR23 to regulate inflammation. J Immunol 2007; 178: 3912-3917
76 Duffield JS, Hong S, Vaidya VS, Lu Y, Fredman G, Serhan CN, Bonventre JV. Resolvin D series and protectin D1 mitigate acute kidney injury. J Immunol 2006; 177: 5902-5911
et al. Advances in liver preconditioning

Pettinelli P, Ponichich J. Increase in long-chain polyunsaturated fatty acid n - 6 / n - 3 ratio in relation to hepatic steatosis in patients with non-alcoholic fatty liver disease. *Clin Sci (Lond)* 2004; 106: 635-643

78 Pierre JL, Fontecave M, Crichton RR. Chemistry for an essential biological process: the reduction of ferric iron. *Biometals* 2002; 15: 341-346

79 Puntarulo S, Gallego M. Forms of iron binding in the cells and the chemical features of chelation therapy. *Mini Rev Med Chem* 2009; 9: 1136-1146

80 Grues E, Toussaint MJ, Niewold TA, Koopmans SJ. Acute phase reaction and acute phase proteins. *J Zhejiang Univ Sci B* 2005; 6: 1045-1056

81 Videla LA, Fernández V, Tapia G, Varela P. Oxidative stress-mediated hepatotoxicity of iron and copper: role of Kupffer cells. *Biometals* 2003; 16: 103-111

82 Cornejo P, Tapia G, Puntarulo S, Gallego M, Videla LA, Fernández V. Iron-induced changes in nitric oxide and superoxide radical generation in rat liver after lindane or thyroid hormone treatment. *Toxicol Lett* 2001; 119: 87-93

83 She H, Xiong S, Lin M, Zandi E, Giuliani C, Tsukamoto H. Iron activates NF-kappaB in Kupffer cells. *Am J Physiol Gastrointest Liver Physiol* 2002; 283: G719-G726

84 Pham CG, Bubici C, Zazzeroni F, Papa S, Jones J, Alvarez K, Jayawardana S, De Smaele E, Cors G, Beaumont C, Torti FM, Torti SV, Franzoso G. Ferritin heavy chain upregulation by NF-kappaB inhibits TNFalpha-induced apoptosis by suppressing reactive oxygen species. *Cell* 2004; 119: 529-542

85 Templeton DM, Liu Y. Genetic regulation of cell function in response to iron overload or chelation. *Biochim Biophys Acta* 2003; 1619: 113-124

86 Theil EC, Eisenstein RS. Combinatorial mRNA regulation: iron regulatory proteins and iso-iron-responsive elements (Iso-IREs). *J Biol Chem* 2000; 275: 40659-40662

87 Ganz T. Hepcidin and iron regulation, 10 years later. *Blood* 2011; 117: 4425-4433

88 Verga Falzacappa MV, Vujic Spasic M, Kessler R, Stolte J, Hentze MW, Muckenthaler MU. STAT3 mediates hepatic iron regulatory proteins and iso-iron-responsive elements by inducing ferric nitrilotriacetate. *Hepatology* 2002; 36: 353-358

89 Moriya K, Miyoshi H, Shinzawa S, Tsutsumi T, Fujie H, Goto K, Shintani Y, Yotsuyanagi H, Koike K. Hepatitis C virus core protein compromises iron-induced activation of antioxidants in mice and HepG2 cells. *J Med Virol* 2010; 82: 776-792

90 Kanki K, Umemura T, Kitamura Y, Ishii Y, Kuroiwa Y, Kodama Y, Itoh K, Yamamoto M, Nishikawa A, Hirose M. A possible role of nrf2 in prevention of renal oxidative damage by ferric nitrilotriacetate. *Toxicol Pathol* 2008; 36: 353-361

91 Calabrese EJ. Converging concepts: adaptive response preconditioning, and the Yerkes-Dodson Law are manifestations of hormesis. *Ageing Res Rev* 2008; 7: 8-20

92 Videla LA. Hormetic responses of thyroid hormone ca

93 Braverman LE, Utiger RD. Introduction to thyrotoxicosis. In: Braverman LA, Utiger RD, editors. *Werner and Ingbar,s The Thyroid: A Fundamental and Clinical Text, New York: Lippincott-Raven Publishers*, 1996: 522-524

94 Bacon BR, Britton RS. Hepatic injury in chronic iron overload. Role of lipid peroxidation. *Chem Biol Interact* 1989; 70: 183-226

95 Buser PT, Wikman-Coffelt J, Wu ST, Derugin N, Parmley WW, Higgins CB. Postsischemic recovery of mechanical performance and energy metabolism in the presence of left ventricular hypertrophy. A NMR study. *Circ Res* 1990; 66: 735-746

96 Pantos C, Mourouzis I, Cokkinos DV. Thyroid hormone as a therapeutic option for treating ischaemic heart disease: from early repercussion to late remodelling. *Vascular Pharmacol* 2010; 52: 157-165

97 Pantos CI, Malliopou lou VA, Mourouzis IS, Karamanoli EP, Paizis IA, Steinberg N, Varondos DN, Cokkinos DV. Long-term thyroxine administration protects the heart in a pattern similar to ischemic preconditioning. *Thyroid* 2002; 12: 325-329

98 Farooqui AA, Horrocks LA, Farooqui T. Modulation of inflammation in brain: a matter of fat. *J Neurochem* 2007; 101: 577-599

99 Munoz JP, Chiong M, Garcia L, Troncoso R, Toro B, Pedrozo Z, Diaz-Elizondo J, Salas D, Parra V, Núñez MT, Hidalgo C, Lavandero S. Iron induces protection and necrosis in cultured cardiomyocytes: Role of reactive oxygen species and nitric oxide. *Free Radic Biol Med* 2010; 48: 526-534

100 Chevion M, Leibowitz S, Aye NN, Novogrodsky O, Singer A, Avizemer O, Bulvik B, Konijn AM, Berenshine E. Heart protection by ischemic preconditioning: a novel pathway initiated by iron and mediated by ferritin. *J Mol Cell Cardiol* 2008; 45: 839-845

101 Metzler B, Jehle J, Theurl I, Lrudwczek S, Obrist P, Pachinger O, Weiss G. Short term protective effects of iron in a murine model of ischemia/reperfusion. *Biometals* 2007; 20: 205-215

102 Brand A, Schonfeld E, Isharel I, Yavin E. Docosahexaenoic acid-dependent iron accumulation in oligodendroglia cells protects from hydrogen peroxide-induced damage. *J Neurochem* 2008; 105: 1325-1335

103 Hidalgo C, Núñez MT. Calcium, iron and neuronal function. *IUBMB Life* 2007; 59: 280-285

104 Brent GA, Larsen PR. Treatment of hypothyroidism. In: Braverman LA, Utiger RD, editors. *Werner and Ingbar,s The Thyroid: A Fundamental and Clinical Text, New York: Lippincott-Raven Publishers*, 1996: 883-887

105 Silverstein SB, Rodgers GM. Parenteral iron therapy options. *Am J Hematol* 2004; 76: 74-78

106 Bayraktar UD, Bayraktar S. Treatment of iron deficiency anemia associated with gastrointestinal tract diseases. *World J Gastroenterol* 2010; 16: 2720-2725

107 Mardones M, Valenzuela R, Romanque P, Covarrubias N, Anghiileri F, Fernández V, Videla LA, Tapia G. Prevention of liver ischemia reperfusion injury by a combined thyroid hormone and fish oil protocol. *J Nutr Biochem* 2011; [Epub ahead of print]

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