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Brain-liver interactions during liver ischemia reperfusion injury: a minireview

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Abstract. The liver is a vital organ, with a wide range of functions. This organ plays an important role in the metabolism, including the glycogen storage, decomposition of red blood cells, plasma protein synthesis, hormone production, and detoxification. The liver is innervated by sympathetic and parasympathetic nerves which are involved in the regulation of the hepatic metabolism. Tissue injury connected with ischemia and reperfusion has been implicated in several clinical settings, including myocardial infarction, brain ischemia, and organ transplantation. Consequences of the liver ischemia reperfusion injury (LIRI) induce first of all an organ failure and afterwards multiorgan system damages that may eventually lead to a death. Many models with an attempt to reduce harmful consequences of the LIRI, directing to develop a variety of prophylactic strategies, has been introduced including models of warm, cold or normothermic ischemia, ischemic pre- and post-conditionings, pharmacological interventions, etc. In spite of the improvements in the medical care and accumulation of a large amount of experimental data concerning the prevention of ischemia and reperfusion related injuries, many destructive processes explanation still remains problematic.

General outline

The liver is the largest single organ in the body that represents major biochemical factory carrying out quantity of synthetic and degradative processes, playing major role in the metabolism of fats, proteins, and carbohydrates (Fleming 1999). In rats, the liver mass represents about 5 % of the total body weight (Martins and Neuhaus 2007). It consists of 4 lobes – middle lobe which is the largest one, left lateral lobe having a rhomboid shape, right lobe which is almost completely covered by the medial lobe, and caudate lobe located behind the left lateral lobe (Martins and Neuhaus 2007). The liver receives about 25 % of arterial blood supply via the hepatic artery, while 75 % of blood flow is represented by venous blood from the gut carried by portal vein, and the bile manufactured by liver carried by the bile duct into the duodenum (Fleming 1999). The liver is innervated by sympathetic and parasympathetic nerves that contain afferent and efferent aminergic, cholinergic, peptidergic, and nitrinergic components. Increasing amount of evidence affirms the importance of the liver innervation in the regulation of hepatic metabolism and hemodynamics (Shimazu 1996). Sympathetic nerves innervating the liver originate in the celiac and superior mesenteric ganglia, which are innervated by sympathetic preganglionic neurons located in the intermediolateral column of the spinal cord (IML). Parasympathetic liver innervation arises from the preganglionic neurons in the dorsal motor nucleus of the vagus (DMV) however, no intrahepatic postganglionic neurons have been identified so far (Berthoud 2004). The liver vagal afferent fibers project to the left nodose ganglion (Berthoud et al. 1992) from which axon processes are directed to the nucleus of the solitary tract (NTS). Sympathetic liver afferents project to the dorsal root ganglion axons which terminate in the dorsal horn of the spinal cord (Berthoud 2004). With the help of multi-synaptic viral

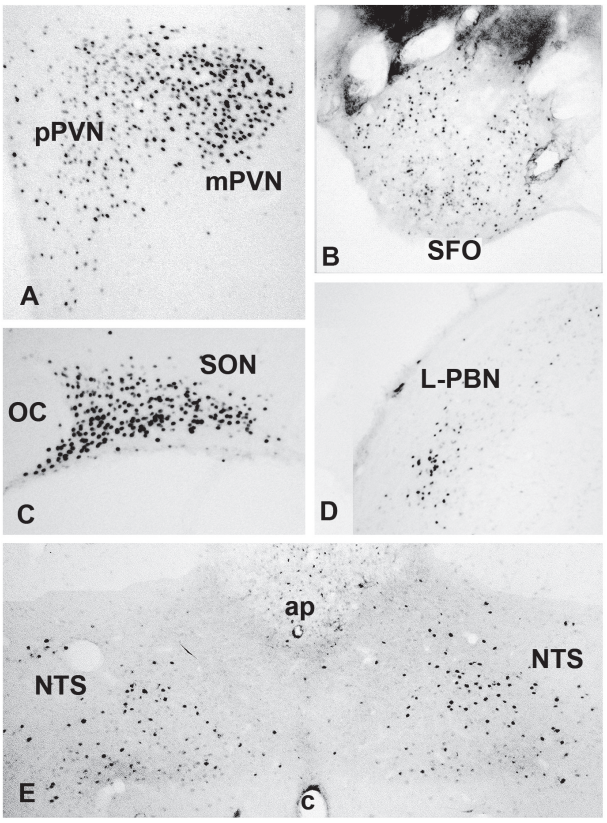

Fig. 1 Fos immunoreactivity in selected brain areas 90 min after ligation of the portal triad. Distinct Fos expression is demonstrated in (A) the magnocellular (mPVN) and parvicellular (pPVN) hypothalamic paraventricular nucleus subdivisions, (B) subfornical organ (SFO), (C) hypothalamic supraoptic nucleus (SON), (D) lateral parabrachial nucleus (L-PBN), and (E) the nucleus of the solitary tract (NTS) and area postrema (ap). Abbreviations: OC – optic chiasm, c – canalis centralis.

tracing methods, different brain regions, involved in the regulation of the liver function, have been characterized. Second-order neurons were detected in areas such as the lateral hypothalamus (LHA), hypothalamic paraventricular (PVN) and suprachiasmatic (SCN) nuclei or retrochiasmatic area (La Fleur et al. 2000). LHA is thought to be predominantly involved in the parasympathetic innervation because its stimulation reduces the appetite and induces series of anabolic responses (Uyama et al. 2004). The PVN regulates sympathetic as well as parasympathetic innervations of visceral organs including liver (Uyama et al. 2004), and SCN is responsible for the maintaining of the circadian rhythms, including basal levels of the plasma glucose (La Fleur et al. 1999). Also neuropeptides like thyrotropin-releasing hormone (TRH) and corticotropin-releasing factor (CRH) have been shown to act in the brain to stimulate or inhibit hepatic blood flow through vagal or sympathetic pathways, respectively (Yoneda et al. 2001). Moreover, vagal pathways are responsible for the central effect of TRH and NPY in the stimulation of hepatic proliferation and ductal bile secretion, respectivelly (Yoneda et al. 2001). It means, dynamic networks of both the endocrine and autonomic nervous systems are involved in the liver function and pathology (Swain et al. 1993; Chida et al. 2006).

Ischemia reperfusion event

Ischemia is characterized by an interruption of the blood flow and consequent lack of oxygen and nutrient supply in organs or tissues. Lack of the energetic substrate induces failure of active transmembrane transport, what causes cell swelling or even necrosis. Dying cells release their intracellular content including alanine aminotransferase (ALT), aspartate aminotransferase (AST) enzymes, serum F protein, glutathione-S-transferase alpha, and malate dehydrogenase that serve as predictive markers of the liver injury (Ozer et al. 2008). Elevated plasma levels of the above mentioned proteins may reflect the extent of the liver damage. By restoring the blood supply, liver is exposed to another insult aggravating injury caused by ischemia (Inglott et al. 2001). After the reperfusion, reactive oxygen species are one of the first elements formed (Zhang et al. 2007), vasoconstriction (Marzi et al. 1994), leukocyte and platelet aggregation within the sinusoids (Jaeschke et al. 1990; Cywes et al. 1993), activation of Kupffer cells, and neutrophils which produce inflammatory cytokines (Colletti et al. 1996) that further worsen the hepatic injury. The most studied substances with large pro-inflammatory activities are tumor necrosis factor alpha (TNF-α) and inteleukins (IL-1β and IL-6) (Montalvo-Jave et al. 2007). Production of these cytokines, including other chemokines and adhesion molecules, is supposed to be controlled by transcription factors nuclear factor kappa B (NFκB) and activator protein 1 (AP-1) which are activated by LIRI too (Baeuerle and Henkel 1994; Bradham et al. 1997). Cytokines initiate and maintain the inflammatory response, resulting in worsening the impact of the reperfusion injury (Fong et al. 1990).

Brain and LIRI

Information about the peripheral inflammation is transferred into the brain. Wang and co-workers (2006)

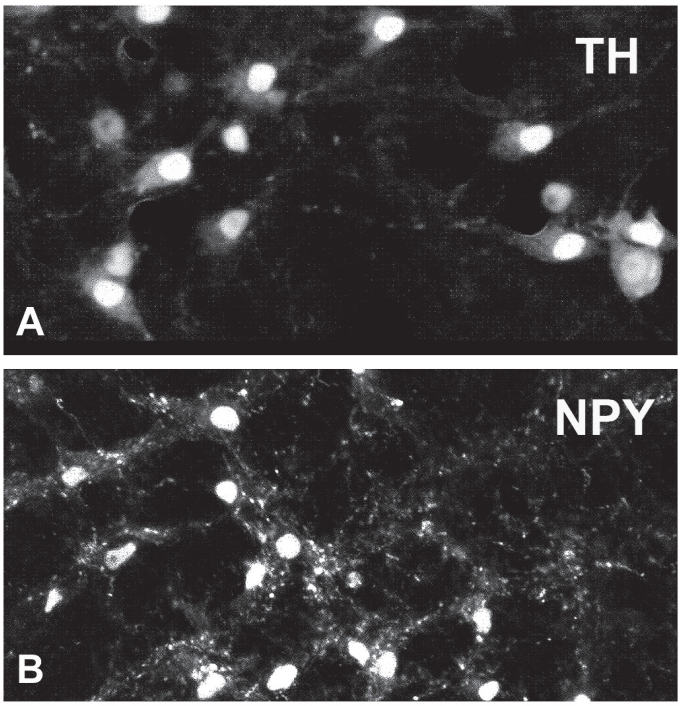

Fig. 2 Phenotypic character of activated neurons 90 min after ligation of the portal triad. Dual immunohistochemical demonstration of Fos/TH (A) and Fos/NPY (B) in the brainstem A1/C1 catecholaminergic area.

have detected, using Fos protein immunostaining (a general marker of neuronal activity), an increased neuronal activation in the hippocampus, cerebral cortex, medulla oblongata, and cerebellum in rats that underwent myocardial ischemia reperfusion injury. In our study (Pirnik et al. 2009) we have characterized more brain areas activated during the LIRI: 1) we have found an increased Fos protein expression in several brain structures (Fig. 1) including the subfornical organ, hypothalamic paraventricular and supraoptic nuclei, suprachiasmatic and arcuate nuclei, locus coeruleus, parabrachial nucleus, nucleus of the solitary tract, and hindbrain A1/C1 catecholaminergic cell groups and 2) we, as the first ones, have also shown the phenotypic character of some of the activated neurons (Fig. 2) including those synthesizing vasopressin (AVP), oxytocin (OXY), tyrosine hydroxylase (TH), corticoliberine (CRH), neuropeptide Y (NPY) and phenylethanolamine N-methyltransferase (PNMT) (Bundzikova et al. 2010). Moreover, these neurons are intergrated in more and today well described functional systems and therefore, their identification may serve as an indicator of pathophysiological responses of the body to LIRI. As we have identified, some of them may be involved in the regulation of osmotic and hemodynamic homeostasis (AVP, OXY, NPY) or responses to stress (CRH, TH, PNMT, OXY) (Bundzikova et al. 2010). However, our observations also call for a caution that activation of brain neurons by LIRI is not only the result of the LIRI itself but it also results of some affiliated events which in this kind of model have to be taken into consideration.

It is evident that bidirectional interactions between the brain and peripheral tissues, including liver (Fig.3), may contribute to both the mental and physical health. Especially the nervus vagus involvement in disorders like obesity, diabetes mellitus, and hypertension has been proven (Curtis and O´ Keefe 2002; Masi et al. 2007). During the last decade it has been shown that neural circuits provide functional control also over the immune responses and that the nervus vagus represents the key structure in so called „inflammatory reflex" (Tracey 2002). The vagus nerve afferent fibers detect the presence of different inflammation markers and relay this information to the brain. Consequently, efferent fibers of the vagus nerve (cholinergic anti-inflammatory pathway) inhibit synthesis and release of the pro-inflammatory cytokines from the immune cells at the periphery (Van Westerloo 2010). Effects of the cholinergic anti-inflammatory pathway have been studied in different diseases, including the liver ischemia reperfusion injury (LIRI), in many experimental animal models.

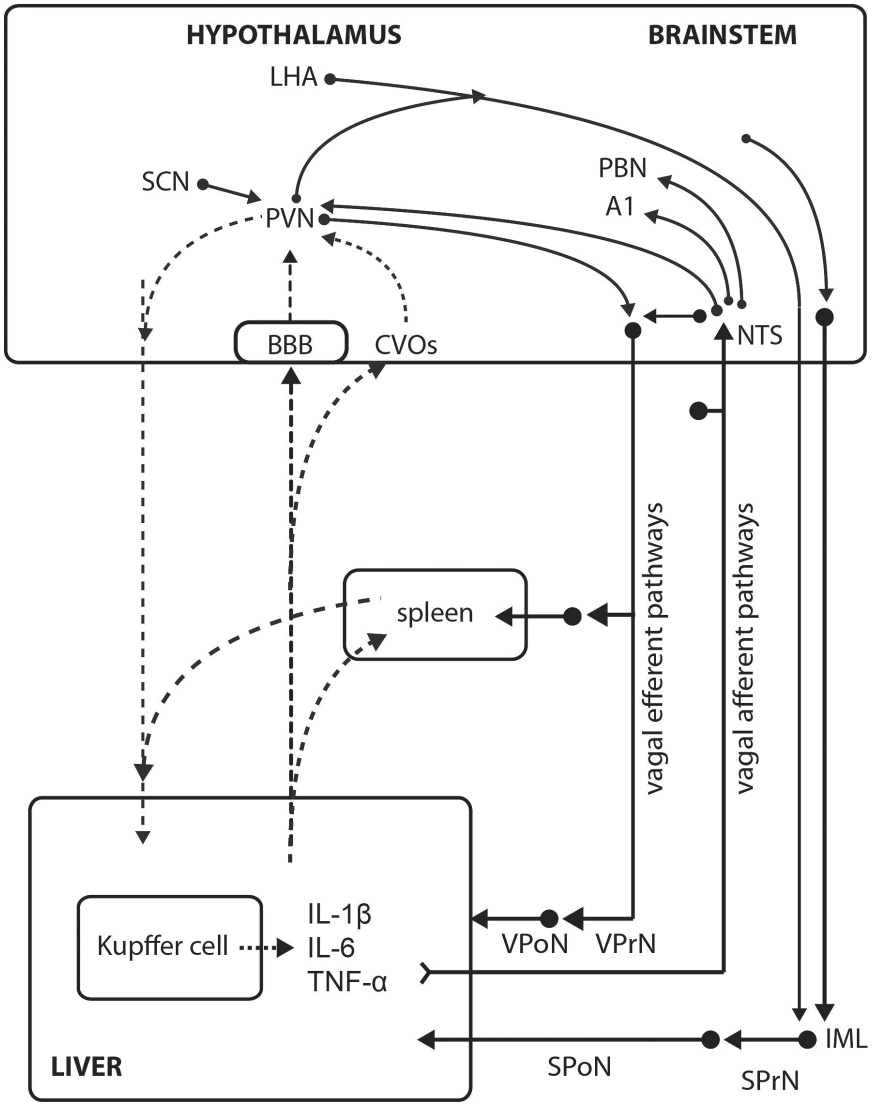

Fig. 3 Outline of the liver, hypothalamus, and brainstem functional interconnections. Signals related to liver activity are transmitted to the brain via nervous (solid line) and humoral (dashed line) pathways. These pathways transmit also signals generated by liver during ischemia-reperfusion injury. These signals include cytokines, changes in water and electrolyte balance, energy production, nociception, and temperature changes. The brain receives these signals at the level of the brainstem and forebrain structures and modulates liver functions by autonomic nerves (solid lines) and neuroendocrine pathways (dashed lines). A1 – A1 noradrenergic cell group; BBB – blood-brain barrier; CVOs – circumventricular organs; IML – intermediolateral cell column; LHA – lateral hypothalamic area; NTS – nucleus of the solitary tract; PBN – parabrachial nucleus; PVN – paraventricular hypothalamic nucleus; SCN – suprachiasmatic nucleus; SPoN – sympathetic postganglionic neuron; SPrN – sympathetic preganglionic neuron; VPoN – vagal postganglionic neuron; VPrN – vagal preganglionic neuron.

Experimental models of LIRI

LIRI has been associated with more clinical situations including hepatectomy performed under temporary inflow occlusion, inflow and outflow occlusions, storage, and implantation of livers for transplantation purposes (Wang et al. 2008). Hepatic ischemia reperfusion injury occurs as a consequence of trauma and hemorrhagic shock as well as temporary clamping of the hepatoduodenal ligament during liver resection (Alchera et al. 2010). So far, more animal models of the LIRI have been developed and tested. Steiner and Martinez (1961)

have studied effects of occlusion of the bile duct, portal vein, hepatic artery or only of their branches. Luo and Dai (1994) have performed occlusion of the portal triad (portal vein, hepatic artery and bile duct) in rabbits. Also models of warm ischemia (blood vessels are clamped without cooling the liver), cold ischemia (blood vessels are clamped and the liver is cooled) or normothermic ischemia have been introduced (Wang et al. 2008; Spiegel and Bahde 2006). It has been shown that the harmful consequences of LIRI i.g. survival of animals, morphological and biochemical markers may be associated with the intensity and duration of the applied liver ischemia (Steiner and Martinez (1961).

LIRI prophylactic strategies

Although the exact mechanisms and details of the LIRI remain to be elucidated, based on the accessible data, a variety of prophylactic strategies have been developed. One is represented by the capacity of a non-lethal ischemia to modulate cell functions by increasing resistence to subsequent lethal ischemia reperfusion (Alchera et al. 2010). This phenomen is termed „ ischemic pre-conditioning" (IP). It has been suggested that the process of IP implies the production of complex proteomic modifications within liver cells (Alchera et al. 2010). Murray and co-workers (1986) have observed that short periods of ischemia and subsequent reperfusion may exert a preventive effect against myocardial injury following ischemia with reperfusion. The same phenomenon has been also reported later in the liver (Peralta et al. 1997; Ishii et al. 2001; Duenschede et al. 2007). Yadav and co-workers (1999) have pointed out in their study that during the ischemic pre-conditioning ischemia and consequent reperfusion periods shorter than 5 min and longer than 15 min fail to induce protection.

Recent studies have shown that also several short periods of ischemia and reperfusion at the beginning of the sustained reperfusion, i.e. ischemic post-conditioning, may provide an effective protection against LIRI (Kin et al. 2004; Fantinelli and Mosca 2007). Wang and co-workers (2008) have compared the effect of ischemic pre- and post-conditionings on the LIRI in rat liver. Results of Wang and co-workers (2008) have shown that both of them are associated with a comparable liver protection. Very promising mechanism to reduce harmful consequences of the LIRI seems to be a pharmacological intervention. Pharmacological treatment with adenosine (Yin et al. 1998), doxorubicin (Ito et al. 2000) or α-lipoic acid (Duenschede et al. 2007) may exert protective effect against LIRI.

Electrical or pharmacological vagal nerve stimulation represents another way how to improve LIRI consequences. There exist more studies indicating that direct electrical stimulation of the vagus nerve may attenuate the myocardial injury and TNF-α synthesis after IRI (Bernik et al. 2002; Mioni et al. 2005; Kawada et al. 2008). Connection of the vagus nerve inhibitory effect with downregulation of pro-inflammatory cytokine TNF-α supports the importance of the cholinergic anti-inflammatory pathway in the development of a systemic inflammation (Tracey 2002). The principal neurotransmitter of the vagus nerve is acetylcholine which binds to the nicotinic and muscarinic receptors. Therefore, agonists of these receptors may represent a promising mean to regulate the cytokine production and inflammation. Wang and co-workers (2003) have shown that α7 nicotinic acetylcholine receptors (α7nAchRs), expressed on macrophages and other cytokine-producing cells, are required for the anti-inflammatory effects of the vagus nerve. They observed that α7nAchRs knockout mice subjected to endotoxemia failed to suppress the systemic TNF-α after the vagus nerve stimulation in contrast with the wild-type mice. Nicotine (an α7nAchRs agonist) pretreatment, in the model of mice renal ischemia reperfusion injury, reduced the tubular damage, TNF-α and high mobility group box 1 (HMG-1) production, neutrophil infiltration in the corticomedullary junction, and apoptosis of tubular epithelial cells (Sadis et al. 2007). Wang and co-workers (2010) have pointed out a protective effect of nicotine in the myocardial íschemia reperfusion injury (nicotine pretreatment reduced the levels of TNF- α, IL-8 and increased level of anti-inflammatory cytokine IL-10). Crockett and co-workers (2006) have studied the influence of preischemic treatment with 2 acetylcholine receptor agonists in the model of LIRI. They again have found reduction in the consequences of the harmful LIRI.

Centrally, the activation the vagus nerve is mediated by brain cholinergic anti-inflammatory pathway which is triggered via MC_4 melanocortin receptors (Guarini et al. 2004). Several melanocortin peptides including adrenocorticotropine (ACTH), α-melanocyte-stimulating hormone (α-MSH), and fragments lacking the C-terminal Arg-Phe sequence, including ACTH (1–24), have a life-saving effect in animals and humans during tissue hypoxia caused

by different shock conditions (Bertolini et al. 1986; Pinelli et al. 1989; Bertolini 1995; Squadrito et al. 1999; Noera et al. 2001), or by prolonged respiratory arrest (Guarini et al. 1997). α-MSH has been shown to be able to reduce the ischemic brain (Huh et al. 1997), renal (Chiao et al. 1997) or small intestine (Hassoun et al. 2002) damage and together with the ACTH reduce the consequences of the short-term coronary ischemia followed by a reperfusion and damage induced by permanent myocardial occlusion in rats (Bazzani et al. 2001). Data obtained from the studies regarding the cholinergic anti-inflammatory pathway indicate that stimulation of the vagal nerve efferent pathways may represent a new approach for the treatment of liver diseases with inflammatory components, including liver ischemia reperfusion injury and liver transplantation. This assertion is strongly supported by recently published data showing that the vagus nerve stimulation improved the function of the recipient kidney in the animal model imitating brain death (Hoeger et al., 2010).

Spleen and LIRI

Spleen has been shown to play an important role in the development of liver injuries in several experimental models such as acute liver injury (Okoshi et al. 1989), liver fibrosis (Miyazaki et al. 1988) or alcoholic liver injury (Tanaka et al. 1992). Most of the blood flow directed to the liver arrives from the spleen thus a large number of lymphocytes and cytokines flow directly into the liver from the spleen (Okuaki et al. 1996). During the LIRI Kupffer cells and neutrophils produce various inflammatory mediators which play role in the hepatic injury (Zhou et al. 1992). Splenic monocytes/macrophages are important cells of mononuclear phagocytic system (Savas et al., 2003) what supports the involvement of the spleen in the organ damage caused by LIRI. The spleen immunohistochemical studies of Okuaki and co-workers (1996) have also showed that mononuclear cells arrive from the splenic monocyte/macrophage populations. Moreover, splenectomy decreases the pressure in the portal vein, which may increase the artery blood supply in the liver, promoting hepatic recovery after LIRI and inhibiting hepatic release of destructive cytokines and oxygen-derived radicals (Jiang et al. 2007). Okuaki and co-workers (1996) and Jiang and co-workers (2007) have confirmed that prior splenectomy, ameliorated pathological changes in the liver morphology, reduced elevated levels of serum ALT, AST, and TNF-α, extent of cell apoptosis, and infiltration of polymorphonuclear cells into the liver. Ito and co-workers (2002) have published that splenectomy performed one day before the hepatic ischemia was not able to suppress the effect of LIRI, protective effect of splenectomia was detectable only when it was done 3 or 5 days before the hepatic occlusion. On the other hand, Okuaki and co-workers (1996) have observed protective effect of the splenectomy performed immediately before the LIRI. All these studies may indicate that splenectomy improves the organ damage caused by the LIRI. However, the accurate mechanism of this process is not clear, but its protective activity is probably mediated also via cholinergic anti-inflammatotry pathway (Jiang et al., 2007). Huston and co-workers (2006) have studied a combined effect of splenectomy and the vagus nerve stimulation in animals with lethal polymicrobial sepsis or endotoxemia. They have observed that stimulation of the vagus nerve failed to inhibit serum HMGB-1 and TNF-α levels in splenectomized animals. These results may indicate that spleen is essential to α7nAchRs-dependent protective anti-inflammatory responses.

Conclusion

Tissue injury connected with ischemia and reperfusion has been implicated in several clinical settings, including myocardial infarction, brain ischemia, and organ transplantation. Consequences of injury caused by LIRI include, first of all, an organ failure and afterwards multiorgan system damages that can eventually leads to a mortality (Eum et al., 2007). In spite of the improvements in the medical care and accumulation of a large amount of experimental data concerning the prevention of ischemia and reperfusion related injuries, many destructive processes explanation still remains to be problematic.

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