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Nitric oxide and chemically induced hepatotoxicity: beneficial effects of the liver-selective nitric oxide donor, V-PYRRO/NO

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Abstract

Nitric oxide (NO) is endogenously produced by the enzyme NO synthase in the cell or pharmacologically delivered to tissues as NO prodrugs. This simple molecule is a potent biological mediator in a myriad of physiological and pathological events. The liver plays a central role in metabolism and immune processes, and is a major target organ influenced by NO. NO production in the liver is usually increased in response to acute insult with hepatotoxicants, and may be decreased during chronic liver diseases. The induction of NO production could be envisioned as an early adaptive response, which may become a mediator of tissue damage when in excess. In this regard, inhibition of endogenous NO synthase has been shown to be beneficial in some cases and detrimental in others. The creation of eNOS and iNOS knockout animals has advanced our understanding of NO function in hepatic response to toxic insults. Knocking endogenous NO production can be beneficial in response to certain toxicants; however, in general it weakens the body's defense mechanisms against toxic insults. A variety of pharmacological NO prodrugs have been developed, and, when used appropriately, most of them have demonstrated beneficial effects in the liver in a variety of pathological settings. In this review, we discuss the relationship between NO and hepatotoxicity, and the beneficial effects of NO donors on the liver, using the liver-selective NO donor, V-PYRRO/NO, as an example to demonstrate that pharmacologically delivered NO could have therapeutic benefits for liver disorders.
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Keywords: Nitric oxide; Hepatotoxicity; NO donor; V-PYRRO/NO; Hepatoprotection; iNOS; eNOS

1. Nitric oxide and the liver

1.1. Multiple and diverse effects of NO in the liver

Nitric oxide (NO), a paracrine-acting soluble gas enzymatically synthesized from L-arginine, is a unique biological molecule that has been implicated in a myriad of physiological and pathological processes. NO has a broad range of biological activities including the

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regulation of vascular tone, blood flow, neurotransmission, signal transduction, anti-microbial defense, immunomodulation, cellular redox status, and hepatocellular apoptosis. Once produced, NO has a short half-life and undergoes spontaneous oxidation to the inactive metabolites nitrite and nitrate (Farzaneh-Far and Moore, 2001).

The liver plays a central role in endogenous hormone metabolism, xenobiotic detoxication, and immune processes, and is a major organ influenced by NO under various liver disease conditions (Chen et al., 2003). NO often has complex and diverse roles in the liver. For example, NO may acts as both an inhibitor or as an agonist in hepatic cell signaling events (Laskin et al., 2001). Similarly, NO can have both pro- and antioxidant actions (Joshi et al., 1999; Fitzhugh and Keefer, 2000), and NO can both induce and inhibit apoptosis in the liver (Kim and Billiar, 2001). The factors dictating whether NO will have beneficial versus harmful effects in the liver include the amount and duration of NO exposure, the type of non-NO related toxic insults, and the pathological status of the liver. This chapter reviews endogenous NO production in the liver in response to various hepatotoxicants, the beneficial and harmful effects of NO synthesis inhibition, the eNOS and iNOS knockout animal models, and the beneficial effects of NO donor prodrugs on chemically induced liver toxicity. The liver-selective NO donor, V-PYRRO/NO, will be used as an example in this review, to demonstrate the diverse impact that NO can have on the liver.

1.2. Increased NO production in response to hepatotoxicants

The body's defense system can synthesize a variety of proteins in response to toxic stimuli, such as metallothionein, heme oxygenase-1 and heat-shock proteins. Increased NO production has also been reported in response to various pathological conditions and toxic insults. For example, NO production in the liver is increased during endotoxemia (Laskin et al., 1995) and ischemic reperfusion (Hierholzer et al., 1998). Overproduction of NO is also observed with hepatotoxicity induced by acetaminophen (Hinson et al., 1998), ethanol (Spitzer et al., 2002), carbon tetrachloride (Weber et al., 2003), concanavalin A (Sass et al., 2002), cadmium (Harstad and Klaassen, 2002), and numerous other agents. Thus, NO overproduction is a consistent finding associated with early hepatotoxicity.

Increased NO production has been proposed to play a role as a proinflammatory mediator to kill damaged hepatocytes in the case of acetaminophen overdose (Gardner et al., 1998) or endotoxemia (Laskin et al., 1995). However, increased NO can also function as an adaptive response to acute hepatic inflammation and early sepsis, since NO serves to maximize tissue perfusion, prevents platelet aggregation and thrombosis, and neutralizes reactive radical species (Farzaneh-Far and Moore, 2001; Farghali et al., 2002; Chen et al., 2003). In addition, NO also has anti-microbial properties, prevents neutrophil activation, and acts as a signal for biosynthesis of hepatoprotective proteins. An appropriate amount of NO production can also have anti-apoptotic effects in hepatocytes (Chen et al., 2003). Therefore, NO overproduction may play a role in cell population restructuring (apoptosis) after toxic insult to the liver (Gardner et al., 1998), while in other instances it acts to reduce apoptosis potentially through maximization of liver perfusion.

Thus, increased NO production in response to hepatotoxicants is a common phenomenon, which could be beneficial or harmful depending on the amount and duration of NO production as well as the type of toxic insult and the pathological status of the liver.

1.3. Inhibition of endogenous NO production has beneficial and adverse effects in the liver

The production of endogenous NO is through the enzyme NO synthetase (NOS) that occurs in several forms including iNOS, which is common throughout tissues, and eNOS which occurs primarily in endothelial cells (Farzaneh-Far and Moore, 2001; Chen et al., 2003). Because of the association of increased NO production with various liver diseases, efforts have been made to reduce endogenous NO production using various NO synthetase inhibitors. Inhibition of endogenous iNOS is beneficial in certain conditions such as endotoxemia and ischemia–reperfusion induced liver injury (Laskin et al., 1995; Hierholzer et al., 1998). However, blocking NO production is not always beneficial, and contradictory results have been reported. For example, in one study inhibition of NO production by the specific iNOS inhibitor aminoguanidine was observed to protect against acetaminophen hep-