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Invited Review Article

Mechanistic review of drug-induced steatohepatitis

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ABSTRACT

Drug-induced steatohepatitis is a rare form of liver injury known to be caused by only a handful of compounds. These compounds stimulate the development of steatohepatitis through their toxicity to hepatocyte mitochondria; inhibition of beta-oxidation, mitochondrial respiration, and/or oxidative phosphorylation. Other mechanisms discussed include the disruption of phospholipid metabolism in lysosomes, prevention of lipid egress from hepatocytes, targeting mitochondrial DNA and topoisomerase, decreasing intestinal barrier function, activation of the adenosine pathway, increasing fatty acid synthesis, and sequestration of coenzyme A. It has been found that the majority of compounds that induce steatohepatitis have cationic amphiphilic structures; a lipophilic ring structure with a side chain containing a cationic secondary or tertiary amine. Within the last decade, the ability of many chemotherapeutics to cause steatohepatitis has become more evident coining the term chemotherapy-associated steatohepatitis (CASH). The mechanisms behind drug-induced steatohepatitis are discussed with a focus on cationic amphiphilic drugs and chemotherapeutic agents.

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1. Introduction

Though many compounds are toxic to the liver, very few are capable of inducing steatohepatitis. The compounds that do cause this toxicity span a variety of therapeutic classes. Steatohepatitis is characterized by intrahepatic accumulation of lipids, metabolic syndrome, and hepatic inflammation. The ability of drugs to lead to the development of steatohepatitis is largely due to off therapeutic target effects which cause mitochondrial damage. The major mechanisms of mitochondrial toxicity involve the inhibition of fatty acid beta-oxidation, oxidative phosphorylation, and mitochondrial respiration, however, the exact mechanisms by which each drug effects these pathways vary. As

Abbreviations: ACADL, acyl-CoA dehydrogenase long chain; ATF4, activating transcription factor 4; CAD, cationic amphiphilic drug; CASH, chemotherapy-associated steatohepatitis; CPT-I, carnitine palmitoyltransferase I; ETF, electron transfer flavoprotein; FOLFIRI, chemotherapy regimen containing 5-fluorouracil, leucovorin, and irinotecan; FOLFIRINOX, 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; GI, gastrointestinal; HADHβ, beta-3-hydroxyacyl-CoA dehydrogenase; MCC, methylcrotonyl-CoA carboxylase; MDH, malate dehydrogenase; MSAD, methylmalonate semi-aldehyde dehydrogenase; MTP, microsomal triglyceride transfer protein; MTX, methotrexate; OCT, ornithine carbamoyl transferase; PDK4, pyruvate dehydrogenase kinase 4; SREBP-1c, sterol response element binding protein 1c.

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beta-oxidation is one of the primary pathways by which lipids are metabolized, the inhibition of beta-oxidation leads to the observed accumulation of lipids within hepatocytes. Inhibition of oxidative phosphorylation and mitochondrial respiration is toxic to the mitochondria and can lead to the release of reactive oxygen species (ROS). Together, the buildup of intracellular lipids and ROS likely causes the formation of oxidized lipids and subsequent inflammation. The ability to concurrently stimulate the accumulation of lipids and ROS is of importance as drugs that solely cause lipid accumulation induce simple steatosis but rarely steatohepatitis.

Several generalized models exist that attempt to explain the development of steatohepatitis, either drug-induced or through non-exogenous mechanisms. The first is the "two-hit" model, which states that the steatohepatitis develops in response to two sequential events; first the accumulation lipids followed by a second injury that stimulates inflammation (Day and James, 1998). The second model states that steatohepatitis is a systemic disease of inflammation shared with atherosclerosis and obesity. In this second model, in variance with the "two-hit" model, accumulation of lipid and inflammation occur simultaneously (Bieghs et al., 2012). With this in mind, drug-induced steatohepatitis falls into the systemic inflammation model as drugs that induce steatohepatitis simultaneously cause both hits, i.e., fat accumulation and secondary injury with inflammation. The detailed mechanisms by which various xenobiotics induce steatohepatitis will be discussed below. Focuses will be placed on cationic amphiphilic drugs (CAD), chemotherapy agents, and two additional compounds, valproic acid and tetracycline, which cause steatohepatitis by mechanisms not shared by CADs and chemotherapeutic agents (Table 1).

Before discussing the previously mentioned compounds, it is warranted to give a brief overview of mitochondrial function due to the key involvement of mitochondrial toxicity in drug-induced steatohepatitis (Fig. 1). Mitochondria are responsible for ATP synthesis, as well as lipid and carbohydrate metabolism. These three functions are all interconnected. Lipid metabolism via beta-oxidation creates acetyl-Coenzyme A (CoA), which is subsequently used in the tricarboxylic acid (TCA) cycle. The utilization of acetyl-CoA in the TCA cycle then drives further beta-oxidation. Beta-oxidation and the TCA cycle both contribute to the electron gradient necessary for mitochondrial respiration and ATP synthesis. Due to the reliance upon each other, the disruption of any of these processes can have downstream effects on all the

Table 1
Mechanisms by which each compound induces the development of steatohepatitis.

Drug	Mechanisms underlying development of steatohepatitis	Reference
Amiodarone	Intracellular drug accumulation important in developing steatohepatitis ($t_{1/2}$ = 14–152 days)	Pfizer (2014)
	Inhibition of phospholipase A	Shaikh et al. (1987)
	Inhibition of fatty acid beta-oxidation	Fromenty et al. (1990)
	Inhibition of CPT-I	Kennedy et al. (1996)
	Drug accumulation in lysosomes prevents phospholipid degradation	Mesens et al. (2012)
	Inhibition of electron transport complexes I, n, m and uncoupling of oxidative phosphorylation	Spaniol et al. (2001)
Perhexiline	Development of steatohepatitis requires chronic dosing and drug accumulation. CYP2D6 polymorphisms increases susceptiblility to drug accumulation	Barclay et al. (2003)
	Inhibition of beta-oxidation	Deschamps et al. (1994)
	Inhibition of CPT-I	Kennedy et al. (1996)
	Drug accumulation in lysosomes prevents phospholipid degradation	Bendirdjian et al. (1982)
	Inhibits electron transport complexes I andll, and uncouples oxidative phosphorylation	Deschamps et al. (1994)
Tamoxifen	May disrupt estrogens ability to increase a cell's capacity for beta-oxidation.	Campbell et al. (2003),
	In Sprague–Dawley rats estrogen treatment leads to the upregulation of PPARa, PPARy, HADHp, CPT-I, and PDK4	Maher et al. (2010)
	Inhibition of HADHP interactions with ERa thereby decreasing the amount of beta-oxidation within the cell	Zhou et al. (2012)
	Tamoxifen does not inhibit CPT-I upregulation in HepG2 cells	Zhao et al. (2014)
	Inhibition of CPT-I activity in isolated liver cells at concentrations above 50 pM	Larosche et al. (2007)
	Accumulates within isolated liver mitochondria	Larosche et al. (2007)
	Intercalates mitochondrial DNA, inhibits mitochondrial topoisomerases, and lowers enzymes involved in mitochondrial respiration	Larosche et al. (2007)
	Increases fatty acid synthesis in HepG2 cells via upregulation of SREBP-lc and SREBP-lc response genes	Zhao et al. (2014)
	Inhibition of electron transport complexes m and IV	Tuquet et al. (2000)
Irinotecan	Clinically shown to induce steatohepatitis though mechanisms still largely unknown	Fernandez et al. (2005)), Vauthey et al. (2006)
	Irinotecan induced steatohepatitis mouse model recently developed	Costa et al. (2014)
	Mitochondrial toxicity induced by intercalation of mitochondrial DNA and inhibition of topoisomerases may play a role	Kosovsky and Soslau (1993)
	CAD structure therefore inhibition of mitochondrial respiration and oxidative phosphorylation may play a role.	Zhang et al. (2014)
	Co-treatment of cultured cells with irinotecan and an inhibitor of electron transport synergistically increases irinotecans cytotoxicity.	
Methotrexate	Clinical risk of developing steatohepatitis increases with large cumulative doses of MTX above 4 g	Arena et al. (2012)
	Polyglutamated metabolite of MTX accumulates within hepatocytes	Kremer et al. (1986)
	Damages GI tract mucosa thereby disrupting intestinal barrier functionality and allowing for bacterial translocation to the liver	Song et al. (2006)
	Increases adenosine release from fibroblasts threefold *in vitro*.	Cronstein et al. (1991),
	Activation of stellate cells by adenosine increases collagen production and decreases the activity of matrix metalloproteases.	Chanet A. (2006)
	Induces mitochondrial toxicity by preventing replenishment of mitochondrial folate stores	Kim et al. (1993)
	Mitochondrial toxicity leads to ROS generation, disruption of the mitochondrial membrane, and caspase-dependent apoptosis	Huang et al. (2005), Tabassum et al. (2010)
Valproic acid	Competitive and non-competitive inhibition of CPT-I	Aires et al. (2010)
	Sequesters cellular stores of free coenzyme A preventing fatty acids from undergoing beta-oxidation	Ponchaut et al. (1992)
Tetracyclines	Large IV doses required to induce steatohepatitis	Bjornsson et al. (1997)
	Accumulaion of hepatic triglycerides via inhibition of MTP	Letteron et al. (2003)
	Decreases cellular beta-oxidation in rats through the down-regulation of PPARa, CPT-I, and fatty acid binding protein	Freneaux et al. (1988), Szalowska et al. (2014)
	Increases fatty acid synthesis in HepaRG cells via upregulation of PPARy and SREBP-lc	Antherieu et al. (2011)
	Doxycycline and minocycline inhibit mTOR and activate ATF4. Activated ATF4 increases ROS production by up-regulating CYP2E1	Bruning et al. (2014), Wang et al. (2014)
	Leads to the carbonylation and decreased activity of enzymes involved in beta-oxidation including ACADL and ETF	Deng et al. (2015)
	Leads to the potential sequestration of free Co A via the carbonylation of OCT, MDH, MCC, and MS AD	Deng et al. (2015)