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9

Up-to-Date Insight About Membrane Remodeling as a Mechanism of Action for Ethanol-Induced Liver Toxicity

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1. Introduction

Hepatocellular death is a key mechanism in alcoholic liver diseases. Although ethanol has been described for many years as capable of increasing membrane fluidity, it is only recently that this fluidizing effect has been reported to be involved in ethanol-induced liver toxicity. In addition, in the last decade, a better understanding of plasma membrane has led to suggest that this membrane is not a random association of lipids, but is rather heterogeneous, with various microstructures enriched in specific components depending on their affinity. Special attention has been paid on lipid rafts that are cholesterol- and sphingolipid- rich microstructures, conferring them higher rigidity compared to other plasma membrane microdomains. As lipid rafts can also activate or suppress cell signaling pathways, lipid raft discovery provides new arguments for several researchers to revisit the fluidizing effect of ethanol by studying the possible ethanol-induced physical and biochemical alteration of lipid rafts. Thus, in this chapter, we have considered to review the capacity of ethanol to induce a membrane remodeling, depicted as an increase in membrane fluidity and alterations of physical and biochemical properties of lipid rafts, and its relationship with ethanol liver toxicity.

2. Membrane fluidity

The Singer-Nicolson fluid mosaic model indicates that membranes consist of a phospholipid bilayer, where lipids, in a fluid phase, act as solvent for proteins (Singer & Nicolson, 1972). In this chapter, membrane fluidity means the relative freedom of motion for membrane components, especially phospholipids, and represents the combination of various types of mobility (Figure 1). Membrane fluidity is principally determined by the acyl chain swinging movement and phospholipid rotation. Thus, short chains and double bonds in acyl chains of phospholipids create spaces in the bilayer and promote membrane fluidization. At the opposite, the rigid steroid nucleus of cholesterol, lying next to the first 9 or 10 carbon atoms of the phospholipid acyl chains, prevents the swinging movement of the acyl chains thereby stiffening membranes. For the evaluation of this membrane parameter, most studies have used either electron paramagnetic resonance (EPR) with spin-labeled fatty acids, or

polarization of fluorescence with hydrophobic fluorescence polarization probes. An increased membrane fluidity for EPR is usually assessed by a decrease of order parameter (S), and for fluorescence, by a decrease of polarization (P), anisotropy (A) or microviscosity (η).

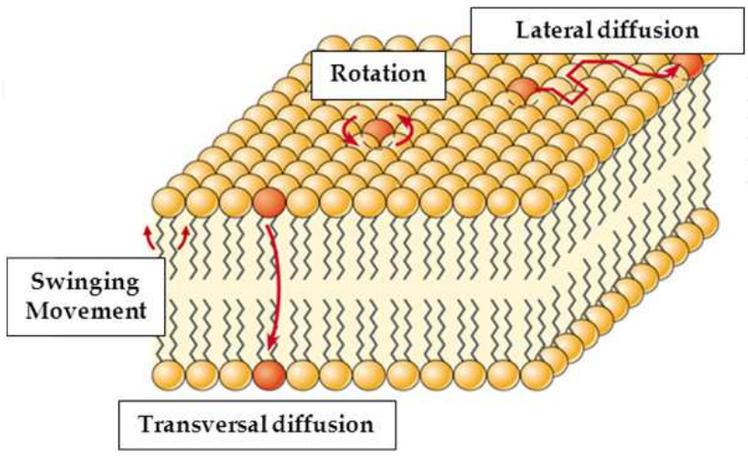


Fig. 1. Different types of mobility of phospholipids.

Any alteration of the optimal range for membrane fluidity has influence on many biological functions such as membrane enzyme and receptor activities, or transmembrane transport processes (Ho et al, 1994; Schachter, 1984; Stubbs et al, 1988). Furthermore, more recently, it was also shown its fundamental role in cell signalling responses to xenobiotic stress (polycyclic aromatic hydrocarbons, cisplatin or ethanol), leading to cell death such as apoptosis (Rebillard et al, 2007; Sergent et al, 2005; Tekpli et al, 2011).

2.1 Plasma liver membranes

Since the end of the seventies, many papers have provided strong evidence that ethanol very rapidly induces a fluidization of membranes as reported by several reviews (Goldstein, 1987; Rottenberg, 1992; Wood & Schroeder, 1988).

2.1.1 Tissue type-dependent effect of ethanol

Using electron paramagnetic resonance, Chin and Goldstein (1977a) were the first to demonstrate the ability of ethanol used at low concentrations (from 20 mM - 40 mM) to increase *in vitro* membrane fluidity of erythrocyte and synaptosomal plasma membranes. In addition, they showed that continuous exposure of mice to ethanol provided in the diet for a short period (8 days) (Chin & Goldstein, 1977b) or by inhalation (3 days) (Lyon & Goldstein, 1983) respectively restored a membrane fluidity near controls or even rigidified membranes in the inner hydrophobic regions, testifying an adaptation. Thus, in alcoholic patients, erythrocytes exhibited a decrease in membrane fluidity (Beaugé et al, 1985; Parmahamsa et al, 2004). However, the effect of ethanol on plasma membranes is different for the liver. Indeed, they become more fluid, mainly in the inner hydrophobic regions, for chronically ethanol-intoxicated rats (Schüller et al, 1984; Yamada & Lieber, 1984) and an increase in fluidity was also observed in plasma membranes isolated from Reuber H35 rat hepatoma

cells (Polokoff et al, 1985) or WRL-68 human hepatic cells (Gutierrez-Ruiz et al, 1995) following a long term treatment with ethanol (3 or 4 weeks). Such an effect could contribute to the special sensitivity of liver to ethanol toxicity. At the opposite, other organelles in the liver did not exhibit any membrane fluidification after ethanol intoxication of rats (Table 1). It should be noted that, when primary hepatocytes isolated from chronically ethanol-treated rats were cultured before the evaluation of plasma membrane fluidity by fluorescence polarization, an increased ordering was observed (Benedetti et al, 1991).

Organelles	Methods	Type of Lipid Bilayer Environne-ment	Membrane Fluidity (compared to controls)	References
Mitochondria	Electron Paramagnetic Resonance	Polar region	=	Waring et al, 1981
	Fluorescence Polarization	Polar region	⇩	Castro et al, 1991
	Fluorescence Polarization	Polar region	⇩	Colell et al, 1997
Microsomes	Electron Paramagnetic Resonance	Polar region	⇩	Ponnappa et al, 1982
	Electron Paramagnetic Resonance	Apolar core region	=	Taraschi et al, 1985
	Electron Paramagnetic Resonance	Apolar core region	=	Aloia et al, 1985
Plasma membranes	Fluorescence Polarization	Apolar core region	⇧	Schüller et al, 1984
	Fluorescence Polarization	Apolar core region	⇧	Yamada and Lieber, 1984

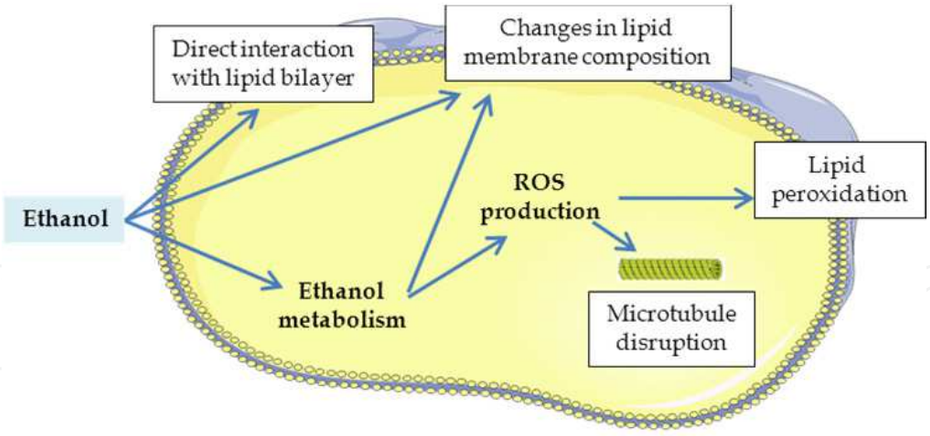
Table 1. Effect of chronic ethanol intoxication on membrane fluidity of various organelles in the liver. (In all experiments, rats were fed a diet containing 36 % of total calories as ethanol for 30 to 40 days.)

Whatever exposure modes (ingestion, inhalation or intraperitoneal injections) (Chin & Golstein, 1977b; Lyon & Golstein, 1983; Johnson et al, 1979), erythrocyte and synaptosomal plasma membranes isolated from ethanol-treated mice did not exhibit an increase in

membrane fluidity after a further *in vitro* ethanol addition in contrast to membranes isolated from untreated mice. Such an *in vitro* resistance was also observed in erythrocyte membranes from alcoholic patients (Beaugé et al, 1985). Even though liver plasma membranes remained more fluid after chronic rat intoxication (Schüller et al, 1984; Yamada & Lieber, 1984) or after long term ethanol treatment of cultured hepatocytes (Gutierrez-Ruiz et al, 1995; Polokoff et al, 1985), these isolated membranes also exhibited an *in vitro* resistance to the disordering effect of a further direct addition of ethanol. Finally, most of the papers quoted in table 1 indicated such a process for microsomes or mitochondria. This phenomenom could be related to several changes in membrane lipid composition (Johnson et al, 1979) *ie* an increase in cholesterol within brain and liver cell membranes in rats (Chin et al, 1978) and in monkeys (Cunningham et al, 1983), an increased ratio of saturated to polyunsaturated fatty acids (Johnson et al, 1979), or reduced concentrations of sialic acid and galactose in the membrane surface of human erythrocytes (Beaugé et al, 1985).

2.1.2 Molecular mechanisms whereby ethanol could increase membrane fluidity

These mechanisms, summarized in figure 2, can occur simultaneously. The first described mechanism was in brain membranes and concerns physical properties of ethanol which allow it to directly interact with the lipid bilayer, thus triggering a direct membrane disorder (Goldstein, 1984; Gurtovenko & Anwar, 2009; Marquês et al, 2011; Rottenberg, 1992). This theory was particularly developed in the field of drug tolerance and physical dependence, but, in the liver, other mechanisms were also described. First, it was proposed that the fluidizing effect of chronic ethanol treatment could be related to changes in membrane lipid composition as acyl chain saturation and cholesterol are well-described to affect membrane fluidity. Thus, Yamada et al (1984) related the increase in membrane fluidity of liver plasma membranes after chronic ethanol feeding to a decrease in cholesterol plasma membrane content by an unknown mechanism. In hepatoma cells chronically exposed to ethanol for 3 weeks, the increase in membrane fluidity of plasma membranes was linked to the elevation of the ratio phosphatidylcholine/sphingomyelin (Polokoff et al, 1985). However, the main distinction of liver is that most of the ethanol metabolism occurs in this organ. Thus, ethanol metabolism appeared to play a key role since blocking ethanol metabolism by methylpyrazole inhibited changes in membrane fluidity both in acute intoxicated primary rat hepatocytes (Sergent et al, 2005), and in chronically treated hepatoma cells (Polokoff et al, 1985). Logically, as ethanol metabolism was involved, our team was interested in looking at the involvement of oxidative stress following an acute ethanol intoxication of primary rat hepatocytes. Using antioxidant such as thiourea (reactive oxygen species (ROS) scavenger) or vitamin E (lipid peroxidation inhibitor), we showed that oxidative stress played a role in the fluidizing effect of ethanol (Sergent et al, 2005). This new mechanism explained how ethanol could very rapidly (30 minutes) increase membrane fluidity since ROS production could be detected as soon as 15 minutes. Several molecular mechanisms can be proposed to explain the influence of oxidative stress on membrane fluidity. First, lipid peroxidation by-products could increase membrane fluidity either by interacting with membrane proteins (Buko et al, 1996; Subramaniam et al, 1997), or more directly by their own rearrangement (Jain et al, 1994; Gabbita et al, 1998). ROS, by oxidizing tubulin could also disrupt microtubule cytoskeleton, thereby increasing membrane fluidity (Yoon et al, 1998; Remy-Kristensen et al, 2000). In our model of primary rat hepatocytes, paclitaxel (a microtubule stabilizer) prevented from the fluidizing effect of ethanol (unpublished data).



(ROS : reactive oxygen species).

Fig. 2. Possible molecular mechanisms for ethanol to increase membrane fluidity.

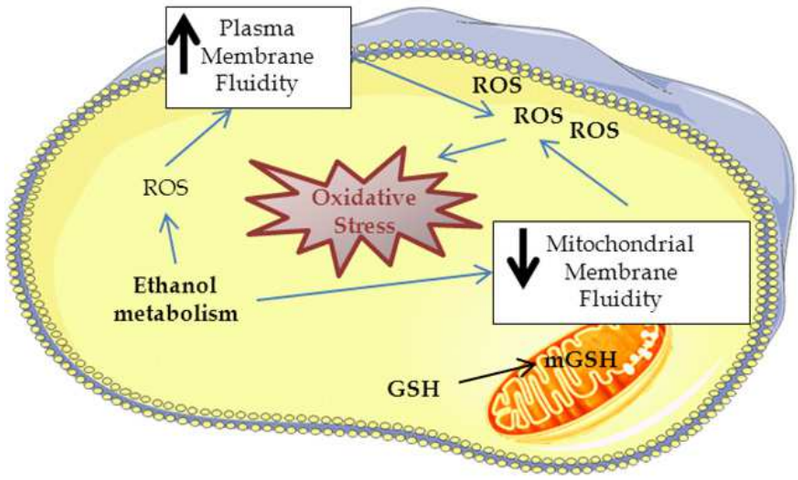
2.2 Liver mitochondria membranes

As shown above, a great body of evidence indicated that, in inner membranes of mitochondria, ethanol intoxication induced a decrease rather than an increase in fluidity. This was demonstrated for chronically intoxicated rats but also with HepG2 human hepatocytes treated with acetaldehyde, a product of ethanol metabolism (Lluis et al, 2003), providing a further proof of the involvement of ethanol metabolism in membrane fluidity changes. In addition, this decrease was related to an elevation of cholesterol content in mitochondria which concerns both outer and inner membranes. Finally, the acetaldehyde stimulation of cholesterol incorporation into mitochondria membranes was attributed to endothelium reticulum stress.

2.3 Membrane pharmacology of ethanol liver toxicity by manipulation of membrane fluidity

Since the eighties, many studies suggested the influence of ethanol fluidizing effect on membrane protein activities (McCall et al, 1989; Mills et al, 1985; Rubin & Rottenberg, 1982). Only recently, researchers became interested in determining the role of membrane fluidity changes in ethanol-induced hepatocellular death. Thus, manipulation of plasma membrane fluidity by exposing primary rat hepatocytes to membrane stabilizing agents (ursodeoxycholic acid (UDCA) or ganglioside GM1 (GM1)) led to the inhibition of ethanol-induced cell death, while fluidizing compounds (tween 20 or A_2C) enhanced it (Sergent et al, 2005). In order to explain how plasma membrane fluidity could affect cell death, oxidative stress was also studied. At the opposite of fluidizing compounds, membrane stabilizing agents were shown to protect from ethanol-induced lipid peroxidation, ROS production and the elevation of another prooxidant factor, namely low-molecular-weight iron. Low-molecular-weight iron consists of iron species that can trigger oxidative stress by catalyzing the formation of a highly reactive free radical, the hydroxyl radical. It should be noted that UDCA and GM1 displayed a protection towards ethanol-induced ROS production only when ROS were evaluated after 1 or 5 hours of incubation with ethanol. At 15 minutes, no protection was afforded by membrane stabilizing agents, unlike the inhibitor

of ethanol metabolism, 4-methyl-pyrazole. This led us to postulate a sequence of events whereby the early ROS formation was mainly due to ethanol metabolism and the late phase to the increase in membrane fluidity (Figure 3). Interestingly, the increased mitochondrial membrane ordering was also associated with the development of oxidative stress. Indeed, stabilizing agents such as S-adenosyl-L methionine (SAME) or taurine conjugate of UDCA (tauroursodeoxycholic acid) protected from glutathione depletion in mitochondria obtained from the liver of rats chronically fed with ethanol (Colell et al, 1997; Colell et al, 2001). Reduced glutathione, the main non protein thiol in cells, plays an important role to detoxify hydrogen peroxide and other organic peroxides in mitochondria. Glutathione depletion in mitochondria made them more sensitive to ROS production and subsequent oxidative stress. Thus, it was demonstrated that the increased mitochondrial membrane microviscosity impaired the glutathione transporter which normally allows the glutathione transport from cytosol to mitochondrial matrix (Coll, 2003; Lluis et al, 2003) (Figure 3).



(GSH : reduced glutathione; ROS : reactive oxygen species).

Fig. 3. Relationship between membrane fluidity and ethanol-induced oxidative stress.

Cholesterol involvement in this process should be pointed out. Indeed, as mitochondrial membrane enrichment in cholesterol was responsible for the decreased mitochondrial membrane fluidity, lovastatin, an inhibitor of hydroxymethylglutaryl coenzyme A involved in cholesterol synthesis, was able to protect hepatocytes from acetaldehyde sensitization to tumor necrosis factor (TNF)α (Lluis et al, 2003). Similarly to membrane stabilizing agents, membrane fluidizer (A_2C) restored the initial glutathione transport rate and mitochondrial content (Coll et al, 2003; Lluis et al, 2003). However, the use of membrane fluidizers should be done with caution since, from our results about the involvement of plasma membrane fluidization in ethanol-induced cell death, it appears that they can be injurious for hepatocytes. At the opposite, UDCA and its conjugates seem to be good candidates for a potential therapeutic use, because, due to their membrane stabilizing properties (Güldütuna et al, 1993), they restore the normality in membrane fluidity for every type of membranes. Thus, in case of ethanol intoxication, they were able to prevent both the increase of plasma membrane fluidity, as we observed in primary rat hepatocytes (Sergent, 2005), and the decrease in mitochondria membranes of hepatocytes from ethanol-fed rats (Colell et al,

2001). In addition, UDCA was also shown to protect rats from the increase in liver plasma membrane fluidity due to chronic ethanol intake and hence from liver lipid peroxidation and necrosis (Oliva et al, 1998). However, although UDCA is a therapeutically relevant bile acid, already used for preventing human primary biliary cirrhosis (Poupon et al, 2003; Corpechot et al, 2011), it did not exhibit any beneficial effect on a 6-month survival of patients with severe alcohol-induced cirrhosis, but possibly because of inappropriate dosage (Pelletier et al, 2003).

3. Lipid rafts

Because of the well-described effect of ethanol on plasma membrane fluidity, it is not surprising that some researchers about alcoholic liver diseases were interested in the possible involvement of lipid rafts in ethanol toxicity. Indeed, plasma membrane is not constituted by a random lipid distribution but rather by a selective lateral lipid segregation due to self-associative properties of sphingolipid and cholesterol, leading to the concept of "lipid rafts" (Simons & Toomre, 2000; Lingwood & Simons, 2010). Thus, lipid rafts are detergent-resistant, sphingolipid- and cholesterol-rich microdomains of the plasma membrane, which form highly ordered spatial nanoscale assemblies separated from other membrane regions composed of more unsaturated and loosely packed fatty acids (Figure 4).

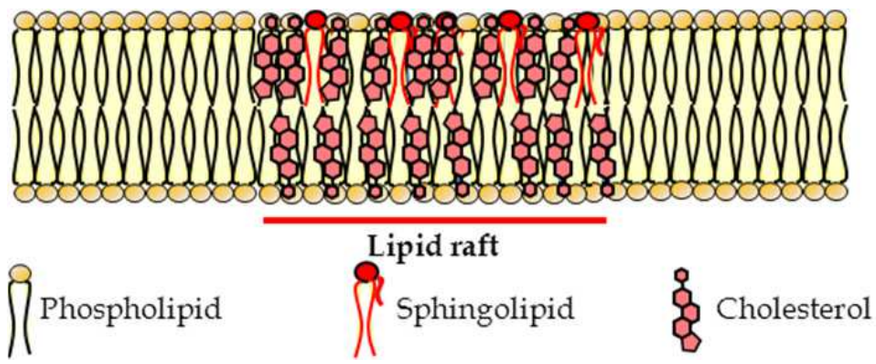


Fig. 4. Schematic representation of a lipid raft (without proteins).

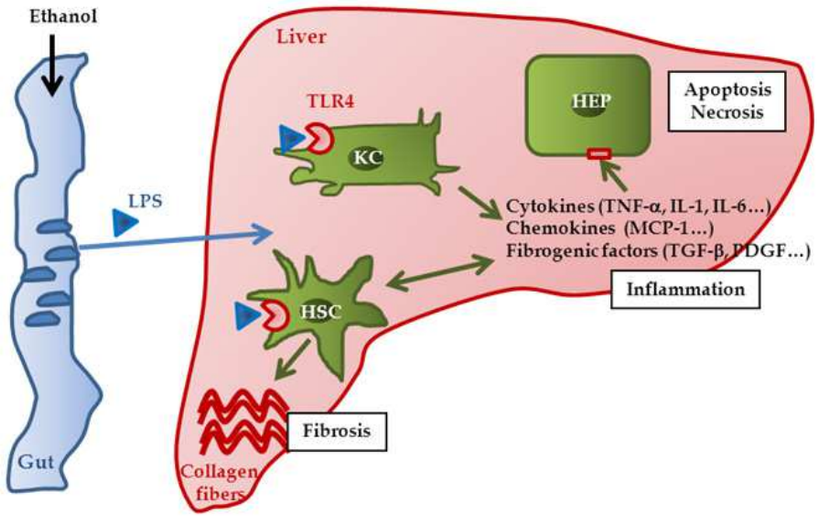
Lipid rafts as nanoscale assemblies are dynamics and after cell stimulation, can coalesced to larger levels to form raft platforms (Harder & Engelhardt, 2004). Concerning proteins, lipid rafts are notably enriched in glycosylphosphatidylinositol (GPI) proteins, receptors such as cell death receptors and Toll-like receptors (TLR), and signaling proteins like mitogen-activating protein kinases, protein kinases C etc. Some proteins are raft residents, whereas others are recruited after cell stimulation with receptor-specific ligands. In addition, based on their mobility, lipid rafts, through their aggregation, can form platforms that assembly many proteins on a same place leading to the formation of a receptor cluster, which can then activate or suppress signaling pathways (Pike, 2003; Schmitz & Orso, 2002). One might suppose that ethanol, through its capacity to increase liver plasma membrane fluidity, can disturb these microdomains and hence, various cell signaling pathways. Consequently, in the last past decade, new investigations were undertaken to possibly link lipid rafts to ethanol toxicity. Researches were conducted in two directions: the main one concerned perturbation of innate immunity *via* TLR4 signaling and the other one, hepatocyte cell death *via* the activation of phospholipase C (PLC) signaling.

3.1 Lipid rafts in the TLR4 signaling dysfunction by ethanol

Several components of innate immunity contribute to the pathogenesis of alcoholic liver disease (Gao et al, 2011). Here, we will mainly focus on lipopolysaccharide (LPS)/TLR4 signaling pathways because of the necessary translocation of TLR4 receptor into lipid rafts for its activation.

3.1.1 Involvement of LPS/TLR4 signaling pathway in alcoholic liver disease

Strong evidence suggest that the immune cells of the liver (phagocytic cells such as neutrophils or resident Küpffer cells, and lymphocytes such as natural killer [NK] cells or T cells) play a crucial role in alcoholic liver disease including steatosis, hepatitis and fibrosis (Suh & Jeong, 2011). Thus, Küpffer cells are main actors in the immune response against endotoxin/lipopolysaccharide (LPS) *via* Toll-Like Receptor type 4 (TLR4) signaling pathway leading to the production of pro-inflammatory mediators such as cytokines (TNF-α, interleukin [IL]-1, IL-6), chemokines (monocyte chemotactic protein-1 [MCP-1]), ROS and profibrogenic factors (transforming growth factor [TGF]-β, platelet-derived growth factor [PDGF]), which subsequently activate hepatic stellate cells for the production of extracellular matrix (Jeong & Gao, 2008) (Gao et al, 2011) (Figure 5). Indeed, it is well established that ethanol intake, by increasing gut permeabilization, allows the uptake of LPS in portal circulation (Parlesak et al, 2000) promoting liver ethanol toxicity (Nanji et al, 1994). In addition, in the liver, TLR4 is also expressed on recruited macrophages, hepatocytes, sinusoidal endothelial cells and hepatic stellate cells (Seki & Brenner, 2008). Consequently, *via* TLR4 signalling, these last cells can also contribute to liver inflammation by releasing proinflammatory cytokines and chemokines. Finally, TLR4 signalling in hepatic stellate cells can also participate to the development of alcoholic fibrosis by enhancing TGF-β signalling (Seki et al, 2007). Therefore, TLR4 receptor appeared crucial in the development of alcoholic liver disease (Gao et al, 2011).



(HEP : hepatocytes; HSC: hepatic stellate cells; KC : Küpffer cells; IL : interleukin; LPS : lipopolysaccharide; MCP-1 : monocyte chemotactic protein-1 ; PDGF : platelet-derived growth factor; TGF: tumor growth factor; TLR4 : Toll-like receptor 4; TNF : tumor necrosis factor)

Fig. 5. Contribution of TLR4 receptor to the pathogenesis of alcoholic liver disease.

3.1.2 Effects of ethanol on the recruitment of TLR4 into lipid rafts

LPS does not bind TLR4 receptor directly, but is rather first bound to cell surface co-receptors, the cluster of differentiation 14 (CD14) and the myeloid differentiation protein 2 (MD-2), without cytoplasmic domains (Fitzgerald, 2004). However, TLR4 is the integrator of cell signalling since it has intracellular signaling domains. Close interactions between these membrane receptors are made possible by their recruitment and assembly within lipid rafts (Schmitz & Orso, 2002; Triantafilou et al, 2002). Thus, CD14 is a glycosyl phosphatidylinositol-linked protein which therefore constitutively resides in lipid rafts, while TLR4 needs translocation into rafts for the complex formation (Dolganiuc et al, 2006). Two features of the ethanol effect on TLR4 and other receptor signaling could be distinguished depending on ethanol concentration. 1) At high concentration (≥ 50 mM), ethanol prevented from LPS-induced redistribution pattern of the co-receptor CD14 within lipid rafts, and from the translocation of TLR4 receptor into rafts (Table 2). This alteration could partly explain why ethanol consumption is recognized as a risk factor for concomitant bacterial or viral infections (Nelson and Kolls, 2002; Szabo, 1999). Dai et al (2005) and Dolganiuc et al (2006) suggested that ethanol, at the concentration of 50 or 86 mM, may disrupt lipid rafts because similar effects were obtained with lipid raft disrupters. However, a protein raft marker, flotillin did not exhibit any alteration and no clear evidence of lipid raft disruption was given, since the cholesterol decrease was detected in culture media instead of lipid rafts. They also attributed changes in partitioning cellular membrane in raft and nonraft structures to the increase in bulk membrane fluidity (Dolganiuc et al, 2006) without checking this influence by the use of membrane stabilizing agents or measuring the increase in membrane fluidity directly in lipid rafts. Their hypothesis would be that ethanol by this way could disrupt lipid protein interactions (Szabo et al, 2007). Only at very high concentrations (200 mM), a lipid raft disruption was really observed in RAW 264.7 macrophages (Fernandez-Lizarbe et al, 2008). However, at 50 mM, in primary rat cortical astrocytes, a partial disruption of lipid raft could be detected suggesting that ethanol at this concentration induced both effects : i) disruption leading to the inhibition of lipid raft – induced cell signalling, and ii) promotion of TLR4 recruitment in lipid rafts (see below)) (Blanco et al, 2008). More recently, it was also demonstrated an ethanol inhibition of lipid raft-mediated T-Cell Receptor (TCR) signalling in human CD4+ T cells and in Jurkat T cells, but no alteration of lipid raft markers was observed suggesting that ethanol had no direct effect on lipid rafts (Ghare et al, 2011). Interestingly, the authors proposed a post-translational modification of proteins to explain the inhibition of protein translocation into lipid rafts. These mechanisms could also be explored for the other models. 2) At lower concentration (≤ 50 mM), mimicking LPS effects both in macrophages and astrocytes, ethanol induced the recruitment of TLR4 into lipid rafts, thus allowing the activation of TLR4 dependent cell signalling (Table 2). A similar process was also observed for IL-1R1 (IL1 receptor 1) (Blanco et al, 2008). Thus, ethanol triggered cytokine and other inflammatory mediator secretion *via* lipid raft-dependent signalling pathway. According to Blanco et al (2008), low ethanol concentrations (10 – 50 mM) may facilitate protein-protein and protein-lipid interactions within the membrane microdomains to promote receptor recruitment into the lipid rafts. Even if this effect has not yet been directly described in the liver, lipid rafts might participate to the mechanisms involved in the enhancement by chronic ethanol treatment of liver inflammation associated with the activation of IL-1R1 receptor in rat liver and hepatocytes (Valles et al, 2003), or TLR4 in immune cells (Szabo & Bala, 2010).

Ethanol Concentration	Cell Type	Ethanol effects on		References
		lipid raft biochemical properties	receptor signalling and inflammation	
86 mM	RAW macrophage like cell line	- Alteration of the redistribution pattern of CD14 in lipid rafts after LPS stimulation	- Decrease in LPS-induced TNFα production - Similar effect with nystatin, a lipid raft disrupter	Dai et al, 2005
50 mM	Chinese hamster ovary cell line (CHO) Primary human monocytes	- Alteration of the redistribution pattern of CD14 in lipid rafts after LPS stimulation - Decrease in LPS-induced TLR4 translocation into lipid rafts -Increase in residual TLR4 in the nonraft fractions - No changes in flotillin, a protein raft marker	- Decrease in LPS-induced TNFα production and NF-kB activation - Similar effects with methyl-β-cyclodextrin, a lipid raft disrupter	Dolganiuc et al, 2006
10 mM **50 mM** **200 mM**	RAW macrophage like cell line Primary mice peritoneal macrophages	-10 mM : CD14 and TLR4 translocation into lipid rafts -50 mM: CD14 translocation into lipid rafts, but at a lesser extent for TLR4 -10 and 50 mM : translocation of proteins associated with TLR4 response into lipid rafts -200 mM : No translocation of TLR4 into lipid rats and disruption of lipid rafts	- Direct production of TNFα (10 mM : by 2.4 fold; 50 mM: by 1.8 fold; 100 mM : no effect)	Fernandez-Lizarbe et al, 2007

Table 2. (Continued)

Ethanol Concentration	Cell Type	Ethanol effects on		References
		lipid raft biochemical properties	receptor signalling and inflammation mediators	
10 mM 50 mM	Primary rat cortical astrocytes	- 10 mM: translocation of IL-1R1 and TLR4 into lipid rafts; recruitment of activated signalling proteins into rafts (P-IRAK and P-ERK) - 50 mM : idem, but at a lesser extent, with a slight disruption	- Expression of IL-1R1 and TLR4 receptors in cell lysates was abolished by lipid raft disrupters (saponin, or methyl-β–cyclodextrin) - Internalization of IL-1R1 receptor in caveosomes	Blanco et al, 2008
25 mM 75 mM	Primary human CD4+ T cells Jurkat T cell line	- Inhibition of PHA or anti-CD23/CD28 antibodies induced Lck, LAT or PLCγ recruitment into lipid rafts - No changes in lipid raft protein marker (flotillin)	Decrease in IL2 expression and down-regulation of TCR signaling	Ghare et al, 2011

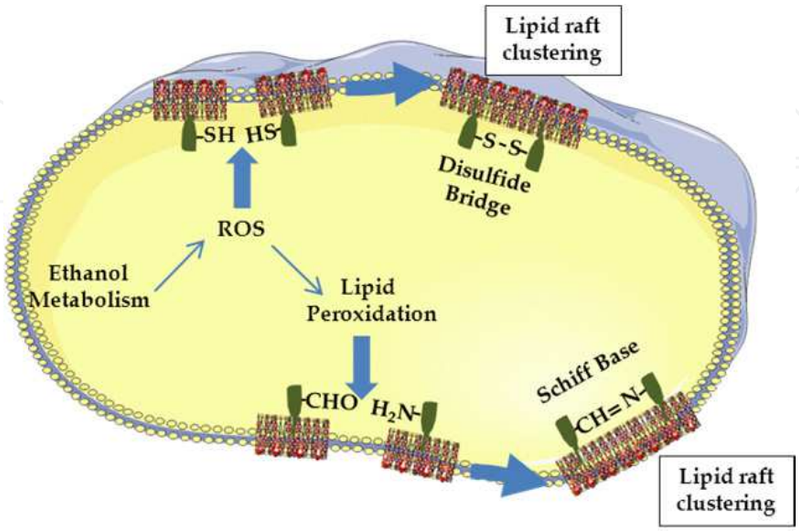
(ERK : extracellular regulated kinase; IL : interleukin; IRAK : interleukin-1 receptor associated kinase; LAT : linker for activation of T cells; lck : lymphocyte-specific protein tyrosine kinase; LPS : lipopolysaccharide; NF-kB : nuclear factor kappa B; PHA : phytohaemagglutinin; PLC: phospholipase C; TCR : T cell receptor; TNF : tumor necrosis factor).

Table 2. Effects of acute ethanol exposure on lipid raft-mediated receptor activation. (In these studies, rafts were isolated by their *in vitro* property to resist to solubilization in non-ionic detergents at low temperature and to float and concentrate in low-density sucrose (Brown & Rose, 1992), leading to raft and non-raft fractions.)

3.2 Lipid rafts in ethanol-induced hepatocyte damage

Another approach was to consider the role of lipid rafts in ethanol-induced oxidative stress. The occurrence of oxidative stress in alcoholic liver disease and its relationship with ethanol liver damage have been extensively documented (Albano, 2008; Cederbaum et al, 2009; De Minicis & Brenner, 2008; Wu & Cederbaum, 2009), but less is known about the possible role of lipid rafts. Thus, it was shown by our team that lipid raft disrupters were able to protect from ethanol-induced ROS production and lipid peroxidation in primary rat hepatocytes (Nourissat et al, 2008). In addition, we have showed for the first time that oxidative changes within lipid rafts are a prerequisite for the oxidative stress to develop in rat hepatocytes.

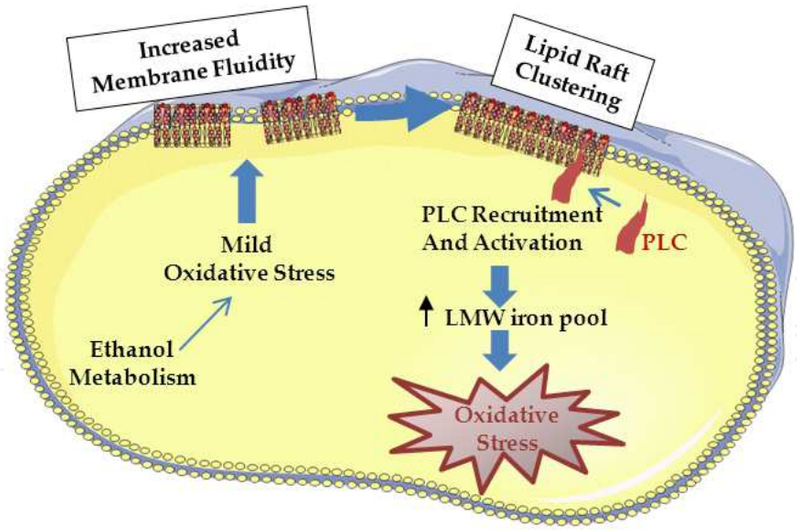
Thus, ethanol metabolism, by producing a rapid and mild oxidative stress, was able to induce oxidative damage within lipid rafts leading to their clustering following protein crosslinkages (Figure 6).



(CHO : carbonyl group; ROS : reactive oxygen species; SH : thiol group)

Fig. 6. Ethanol-induced lipid raft clustering *via* oxidative stress and protein crosslinkage.

Protein crosslinkages were obtained by the formation of disulfide bridges from two intermolecular thiol (SH) groups from several rafts, and by the formation of adducts with malondialdehyde, a well-known product of lipid peroxidation in ethanol treated-rat hepatocytes (Nourissat et al, 2008). This aldehyde like 4-hydroxynonenal can react with nucleophile residues in proteins to form carbonyl groups which then may form Schiff base with a lysine of another protein. Such a protein can be included in another raft leading to raft clustering (Figure 6). Interestingly, according to experiments performed on the translocation of TLR4 (see above) which proposed a role for membrane fluidity without fully demonstrating it, we expressly proved the involvement of the fluidizing effect in the ethanol-induced lipid raft clustering by the use of membrane stabilizer or fluidizers. In addition, ethanol was shown to be able to fluidize lipid rafts, but at a lesser extent compared to bulk membranes. These results also confirmed our previous results which showed the pivotal role of the increased membrane fluidity in ethanol-induced cell death of rat hepatocytes (Sergent et al, 2005), thereby emphasizing on the contribution of membrane remodeling in ethanol liver toxicity. Finally, lipid raft clustering also participated to the activation of phospholipase C-γ-dependent signaling pathway. Indeed, this clustering induced translocation of phospholipase C-γ into rafts, which induced elevation of low-molecular-weight-iron, a potent prooxidant factor, and hence, lipid peroxidation. To summarize, ethanol metabolism, by producing a mild oxidative stress can rapidly affect both membrane fluidity and lipid rafts, thus promoting lipid raft aggregation (Figure 7). Then, this lipid raft clustering, by activating phospholipase C-γ dependent signaling pathway, may in turn trigger amplification of oxidative stress and cell death (Figure 7).



(LMW iron: low molecular weight iron; PLC: phospholipase C)

Fig. 7. Amplification of oxidative stress *via* lipid raft clustering during acute ethanol intoxication of rat hepatocytes.

In this context, new therapeutic approach, called membrane lipid therapy (Escriba et al, 2006), could be a very effective strategy to protect hepatocytes from membrane-dependent oxidative damage in alcoholic liver damage, especially as an increasing body of evidence indicated that some dietary compounds such as plant flavonoids (Tarahosky et al, 2008) or fatty fish long-chain polyunsaturated n-3 fatty acids (n-3 PUFAs) (Wassal & Stillwell, 2009) might modify physical and chemical properties of lipid rafts. Thus, n-3 PUFAs have been extensively described as efficient modifiers of lipid and protein composition of lipid rafts in many cell types such as T lymphocytes (Fan et al, 2004; Stulnig, 2001), Caco-2 cells (Duraisamy et al, 2007), retinal vascular endothelial cells (Chen et al, 2007) and macrophages (Wong et al, 2009). In this context, the nutrional significance of lipid rafts has been recently pointed out (Yaqoob and Shaikh, 2010).

4. Conclusion

Taken altogether, these studies show that physical alterations of membranes (changes in membrane fluidity and microstructures) can be considered as an additional mechanism involved in ethanol liver toxicity. It is only in the last past decade that membrane remodeling appeared to be linked to ethanol liver toxicity (Figure 8). Therefore, further studies are needed in order to determine the role of lipid rafts in chronic ethanol intoxication, to further explore the downstream cell signaling after lipid raft clustering such as pathways involved in the elevation of low-molecular weight iron cell content, or to understand whether receptor recruitment in lipid raft might participate to alcoholic liver disease. In addition, other investigation should shed light on the possible beneficial effect of the modulation of membrane fluidity and lipid raft. Thus, statins that are already currently used in patients suffering from hypercholesterolemia, have demonstrated their efficiency to protect hepatocytes from acetaldehyde sentization to TNF (Lluis et al, 2003), and might also be proposed to disrupt lipid rafts. Finally, nutritional compounds such as plant flavonoids

or fatty fish long-chain polyunsaturated n-3 fatty acids might represent a new therapeutic approach for patients with alcoholic liver disease based upon modulation of the membrane structures.

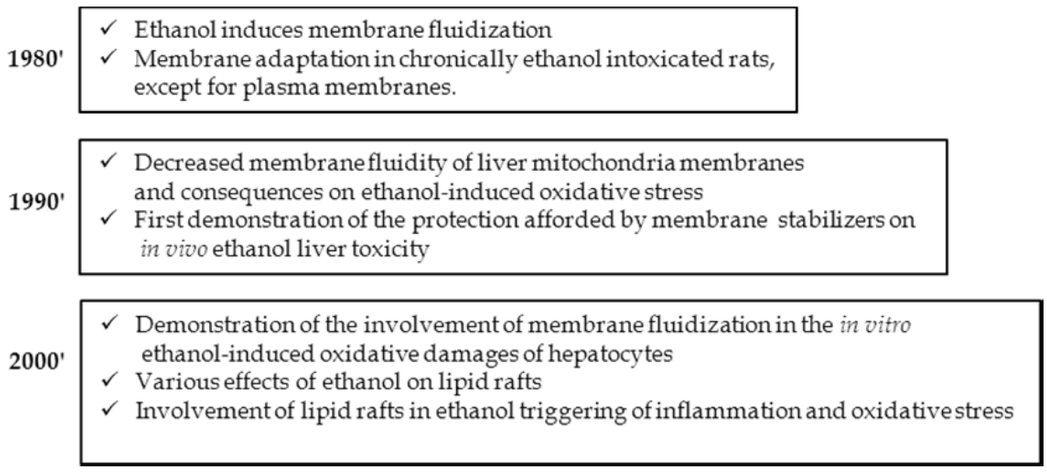


Fig. 8. Evolution of the "membrane remodelling" concept for alcoholic liver diseases.

5. Acknowledgement

The authors gratefully acknowledge IREB (Institut de Recherches Scientifiques sur les Boissons, Paris, France) for its financial support. They also wish to thank "Région Bretagne", which provided a grant for Fatiha Djoudi. The authors are also very grateful to Martine Chevanne for her skilfull technical assistance.

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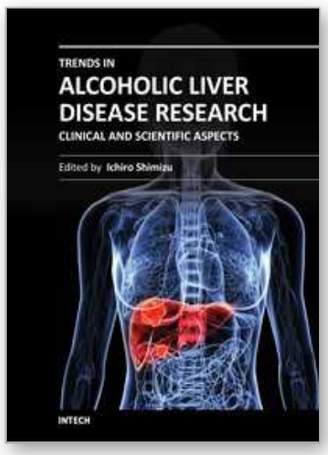

Trends in Alcoholic Liver Disease Research - Clinical and Scientific Aspects

Edited by Dr. Ichiro Shimizu

ISBN 978-953-307-985-1
Hard cover, 220 pages
Publisher InTech
Published online 11, January, 2012
Published in print edition January, 2012

Alcoholic liver disease occurs after prolonged heavy drinking. Not everyone who drinks alcohol in excess develops serious forms of alcoholic liver disease. It is likely that genetic factors determine this individual susceptibility, and a family history of chronic liver disease may indicate a higher risk. Other factors include being overweight and iron overload. This book presents state-of-the-art information summarizing the current understanding of a range of alcoholic liver diseases. It is hoped that the target readers - hepatologists, clinicians, researchers and academicians - will be afforded new ideas and exposed to subjects well beyond their own scientific disciplines. Additionally, students and those who wish to increase their knowledge will find this book a valuable source of information.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Odile Sergent, Fatiha Djoudi-Aliche and Dominique Lagadic-Gossmann (2012). Up-to-Date Insight About Membrane Remodeling as a Mechanism of Action for Ethanol-Induced Liver Toxicity, Trends in Alcoholic Liver Disease Research - Clinical and Scientific Aspects, Dr. Ichiro Shimizu (Ed.), ISBN: 978-953-307-985-1, InTech, Available from: http://www.intechopen.com/books/trends-in-alcoholic-liver-disease-research-clinical-and-scientific-aspects/up-to-date-insight-about-membrane-remodeling-as-a-mechanism-of-action-for-ethanol-induced-liver-toxi

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