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Disrupted VLDL Features and Lipoprotein Metabolism in Sepsis

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1. Introduction

Gram-negative sepsis is an increasingly clinical syndrome triggered by exposure to bacterial lipopolysaccharide (LPS) or endotoxin. It is associated with a plethora of physiological and biochemical changes, known as acute-phase response (APR), including disturbances in serum lipid and lipoprotein levels (Khovidhunkit et al., 2004). Within the blood, LPS is extracted by the acute phase reactant LPS-binding protein (LBP) and transferred to CD14 receptor on monocytes and macrophages. The CD14 associates with Toll like receptor 4, myeloid differentiation-2 and other proteins forming a receptor cluster that leads to LPS-induced activation (Triantafilou & Triantafilou, 2005), resulting in the release of soluble mediators, such as proinflammatory cytokines.

Kupffer cells (KC), the resident macrophages in the liver, secrete cytokines, particularly tumor necrosis factor α (TNF- α) and the interleukins (IL) IL-6 and IL-1 β , that act as paracrine factors on neighboring hepatocytes and promote many of the metabolic changes that accompany the acute-phase response. One of the most striking changes associated to sepsis is the accumulation of triglycerides (TG) within very low density lipoprotein (VLDL) in the plasma, partly ascribed to an increased hepatic VLDL production and a decreased peripheral metabolism driven by pro-inflammatory cytokines. These metabolic alterations, clinically termed as the “lipemia of sepsis”, have been postulated to be components of the innate defensive reaction against infection (Harris et al., 2000).

In this chapter we summarize the actual knowledge on sepsis induced alterations in VLDL metabolism, lipids and apoB availability and the involvement of inflammatory mediators.

2. Hiperlipemia of sepsis

Elevation of plasma lipid levels is an early hallmark of sepsis, clinically defined as lipemia of sepsis. The rise in circulating lipids is mainly caused by a rapid accumulation of triglycerides within very low density lipoproteins (Esteve et al., 2005; Khovidhunkit et al., 2004), although other lipids such as non-esterified fatty acids coming from peripheral tissue lipolysis (Khovidhunkit et al., 2004), or cholesterol, in the case of rodents, can also be elevated (Feingold et al., 1993). However, decreases in cholesterol associated to high density lipoproteins (HDL) have been reported as a characteristic associated to sepsis in primates and rodents (Khovidhunkit et al., 2004).

The accumulation of VLDL particles in plasma is attributable to complex disturbances in their metabolism, including increased hepatic production (Feingold et al., 1992; Khovidhunkit et al., 2004; Lanza-Jacoby et al., 1998) and depressed peripheral clearance in the bloodstream by lipoprotein lipase (LPL) depending upon the dose (Feingold et al., 1992; Khovidhunkit et al., 2004; Lanza-Jacoby et al., 1998). Initially, the sepsis-induced hypertriglyceridemia was thought to constitute a mechanism for supplying high-energy substrates to cells involved in host defence (Hardardottir et al., 1994). However, it is increasingly believed that TG-rich lipoproteins are also components of an innate, non-adaptive host immune reaction against infection in humans and animal models (Barcia & Harris, 2005; Harris et al., 2000; Harris et al., 2002).

Both in vitro (Levels et al., 2001; Van Lenten et al., 1986) and in vivo (Kitchens et al., 2003) studies have demonstrated that all lipoprotein classes are able to bind LPS, through their phospholipid (Kitchens et al., 2003) or apolipoprotein (Levels et al., 2001; Vreugdenhil et al., 2001) components, in such a way that lipoprotein-bound LPS is subsequently cleared from the circulation by hepatic parenchymal cells (Harris et al., 2002). Most of the LPS-binding ability corresponds to HDL particles (Levels et al., 2001); however, when levels of VLDL are increased and HDL diminished, as may occur in endotoxemia, the binding appears to shift towards VLDL (Kitchens & Thompson, 2003; Vreugdenhil et al., 2001) and partially depends on interacting with apolipoprotein B (apoB) (Vreugdenhil et al., 2001). Therefore, higher secretion levels of VLDL may be regarded as a protective mechanism against infection. We have shown in LPS-treated rats that plasma VLDL-apoB is rapidly elevated, and this can represent a defence mechanism to neutralize and remove LPS from the circulation (Fig. 1).

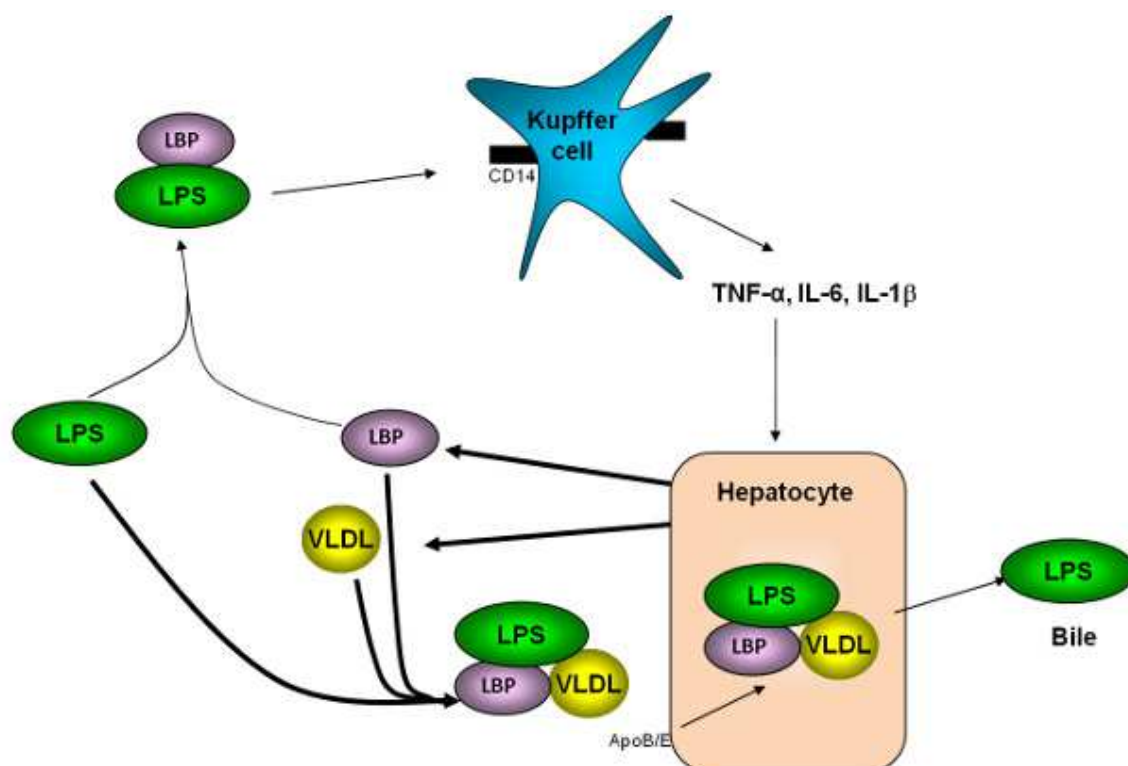


Fig. 1. Proposed role of VLDL in the host inflammatory response. Inflammatory mediators released from Kupffer cells act on hepatocytes inducing the production of VLDL and the synthesis of APR proteins, among them LBP. LBP mediates the binding of LPS to VLDL, the complex is taken up by the hepatocyte and LPS is eliminated through the bile.

Notwithstanding the beneficial role of VLDL, many of the sepsis-associated changes in lipoprotein characteristics and metabolism are similar to those promoting atherogenesis, and has been proposed that the APR associated changes in lipoproteins can be one possible link between infection/inflammation and atherosclerosis. During acute phase reaction, apart from changes in HDL-cholesterol, alterations in HDL associated proteins have been reported. These changes alter cholesterol reverse transport, leading to diminished HDL-cholesterol, and reduce their antioxidant properties (Esteve et al., 2005; Khovidhunkit et al., 2004). In fact, following acute infection low density lipoproteins (LDL) become more susceptible to oxidation (Memon et al., 2000).

One factor that may influence lipoprotein metabolism and is known to be altered during sepsis is food intake (Grunfeld et al., 1996). In order to avoid this variability, animals are food-deprived from the time of administration of endotoxin.

We have shown that endotoxin administration to fasted rats induced hipertriglyceridemia in a time-dependent pattern, related to different systemic fuels (Bartolome et al., 2010). Metabolic background is an important factor contributing to the sepsis-promoted VLDL abundance. We have demonstrated a biphasic response to endotoxin in systemic fuels of fasted rats, with two 12 h differentiated phases. We found that during the first phase serum fatty acids were markedly increased and glucose levels decreased, whereas in the second period hyperglycemia was recorded and fatty acid levels were bellow controls. Impaired glucose metabolism has been reported (McGuinness, 2005). During the second phase of the response we detected increased levels of insulin, that together with the high glucose levels indicate the reported sepsis induced insulin resistance (Andersen et al., 2004). It is well known that overproduction of VLDL is a characteristic of insulin-resistant states (Adeli et al., 2001).

	mean diamenter (nm)	Triglycerides		Cholesterol	
		8 h	18 h	8 h	18 h
VLDL	31,3-64	8,21**	3,16**	3,29***	2,24*
large	44,5-64	9,21***	2,74*	4,69***	2,37*
medium	36,8	6,62***	4,26**	2,89***	2,27*
small	31,3	5,83**	4,18**	1,76	2,00
LDL	16,7-28,6	3,66**	2,88**	0,97	1,36
large	28,6	4,37**	3,49*	1,37	1,78
medium	26,5	3,35**	2,87*	1,19	1,63
small	23	3,08**	2,61*	1,05	1,48
very small	16,7-20,7	3,82**	2,42**	0,83	1,21
HDL	7,6-15	4,64**	1,53*	0,98	0,72*
very large	13,5-15	7,28**	1,93**	1,11	0,72
large	12,1	5,78**	1,80**	1,03	0,69**
medium	10,9	4,15**	1,50**	0,79*	0,75**
small	9,8	4,84***	2,13**	0,83	0,76**
very small	7,6-8,8	4,12**	1,24	0,93	0,79*

Table 1. Fold-changes induced by LPS administration in triglyceride and cholesterol concentration in lipoprotein classes. Rats were injected with LPS and blood collected for lipoprotein triglyceride and total cholesterol measurements.

We analyzed the lipoprotein lipid profile in serum of rats after 8 or 18 h of LPS treatment (Table 1). We found that hypertriglyceridemia was associated with different VLDL, LDL and HDL subclasses depending on the metabolic background of the APR. Although TG increased in all lipoprotein classes, VLDL particles were the major contributors. We did find transient proatherogenic changes in VLDL particles. During the first phase of the APR hypertriglyceridemia was predominantly associated to large VLDL, which were increased 8 fold after 8 h (Bartolome et al., 2010). These large TG-rich VLDL particles, more than normal VLDL, are able to cross the endothelial barrier and interact with lipoprotein receptors in macrophages, initiating a sequence of events that result in the atherosclerotic lesion and, in addition they give rise to small-dense atherogenic LDL (Gianturco et al., 1998; Ginsberg, 2002; Taskinen, 2003). In addition, large TG-rich VLDL were also enriched in cholesterol, making them more proatherogenic.

In the second phase, the rise in serum VLDL-TG corresponded mainly to medium and small VLDL particles. Endotoxin did not affected serum total cholesterol, however changes occurs in lipoprotein subclasses. Total cholesterol increased in large and medium VLDL and HDL-cholesterol levels fell in all HDL subclasses.

3. Altered VLDL metabolism in sepsis

The assembly of VLDL particles is a complex and highly regulated process that occurs in the secretory pathway of hepatocytes. It represents an active export process of fuel carbons, mainly in the form of TG, and is an important route for cholesteryl ester and phospholipid secretion to the circulation. The biogenesis of VLDL has been mostly described as a two step process depending on the cellular availability of lipids, such as triglycerides, phospholipids, cholesterol, and cholesteryl esters, and it is absolutely dependent on the provision of functional apoB, which, in rodents, may be either the full length apoB-100 or the truncated form of apoB-48 (Davidson & Shelness, 2000). Firstly, during translocation to the lumen across the endoplasmic reticulum (ER) membrane, nascent apoB is lipidated by the essential chaperone microsomal triglyceride transfer protein (MTP) (Gordon & Jamil, 2000; Hussain et al., 2003; Liang & Ginsberg, 2001), originating a relatively small, dense, TG-poor lipoprotein particle. In the second stage, bulk of lipidation and final maturation of lipoprotein precursor occur in the ER and post-ER compartments to form mature VLDL (Gusarova et al., 2003; Kulinski et al., 2002). It is known that when MTP activity is low, or when lipid availability or synthesis is reduced, apoB is cotranslationally targeted for ER-associated degradation by both proteasome-dependent and non-dependent pathways (Fisher et al., 2001; Fisher & Ginsberg, 2002; Ginsberg & Fisher, 2009).

The apoB gene has been considered to be constitutively expressed (Pullinger et al., 1989) and VLDL assembly regulation as a post-transcriptional event. However, increasing evidence from in vivo and in vitro studies over the last years has shown changes in hepatic steady-state mRNA levels for apoB in several pathophysiological conditions, particularly under a variety of inflammatory conditions (Jura et al., 2004; Yokoyama et al., 1998).

VLDL secretion rate and composition can be modulated by a variety of factors, such as nutritional state (Gibbons & Burnham, 1991), endotoxin and proinflammatory cytokines (Aspichueta et al., 2006; Bartolome et al., 2007; Perez et al., 2006). Different mechanisms may be involved in the sepsis enhanced VLDL secretion (Fig. 2).

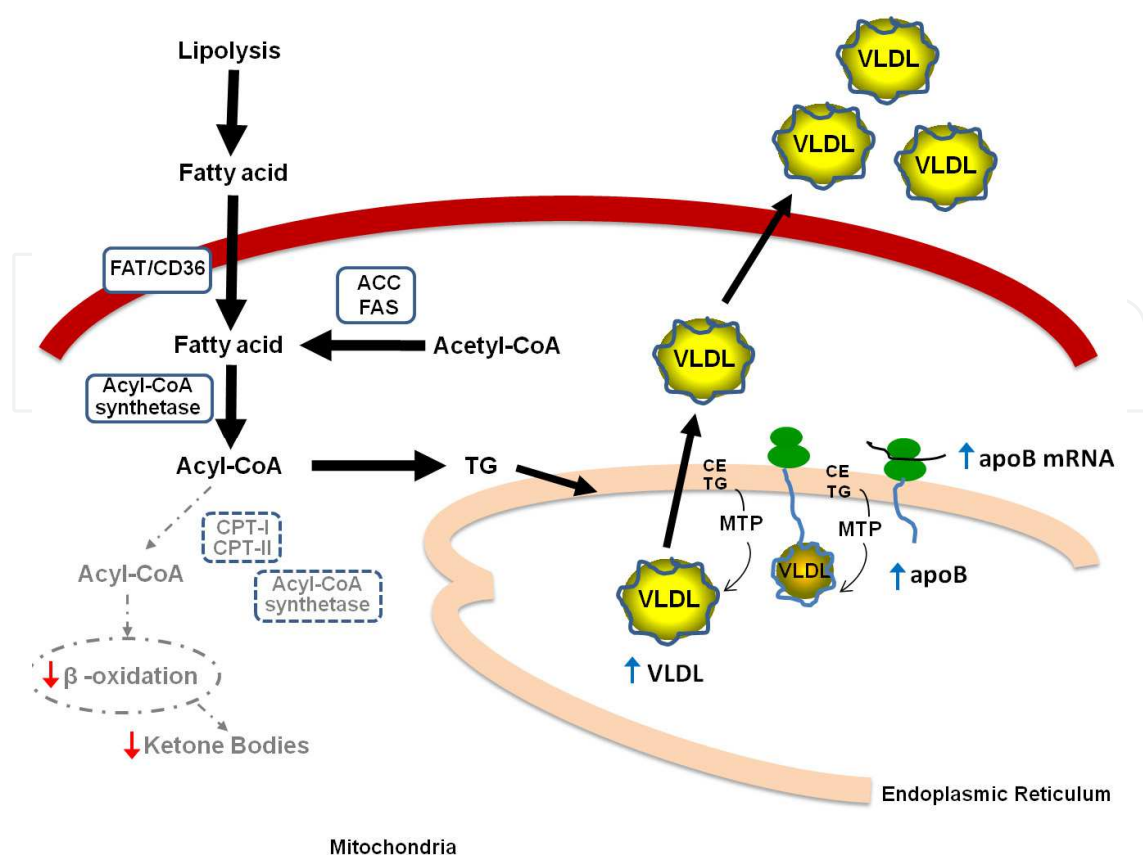


Fig. 2. Model of VLDL assembly and secretion during sepsis. FAT, fatty acid translocase; FAS, fatty acid synthase; ACC, Acetyl-CoA carboxylase; CPT, carnitine acyltransferase. Solid and blue arrows indicate increases, discontinuous and red arrows indicate decreases.

Our results suggest that specific mechanisms are involved in the temporal response to sepsis. In LPS treated rats we found that both fatty acids and hypertriglyceridemia, associated with VLDL-TG, peaked after 8 hours of endotoxin contact. During inflammation adipose tissue lipolysis is activated by pro-inflammatory mediators (Khovidhunkit et al., 2004; Zu et al., 2009) providing fatty acids for hepatic triglyceride synthesis, thus promoting VLDL secretion (Lanza-Jacoby et al., 1998). It has been reported that LPS enhance the expression of fatty acid translocase FAT/CD36, involved in fatty acid uptake (Memon et al., 1998a) and that endotoxin and cytokines suppressed mitochondrial acyl-CoA synthetase expression and activity (Memon et al., 1998b) but enhanced microsomal acyl-CoA synthetase. In addition, LPS administration to rats led to reduced carnitine acyltransferase I, lower ketogenic capacity (Takeyama et al., 1990) and decreased levels of serum ketone bodies (Bartolome et al., 2010). Evidences also established a relationship between increased de novo fatty acid synthesis and enhanced secretion of VLDL-TG in rodents treated with LPS or cytokines (Feingold et al., 1992; Lanza-Jacoby & Tabares, 1990). Taken all together, high amounts of fatty acids are directed away from mitochondrial oxidation and are available for their esterification into TG and secreted within VLDL. However, previous works done in our laboratory did not support the proposed hypothesis since levels of fatty acid synthase mRNA or rate of TG synthesis measured as the incorporation of [3 H]acetate or [3 H]oleate did not change after 18 h of LPS treatment (Aspichueta et al., 2006). The high availability of lipids in the septic hepatocyte would protect apoB from degradation leading to an increased number of secreted VLDL particles (Phetteplace et al., 2000). In fact,

we detected an elevation of 5 fold in the number of circulating VLDL particles, measured as apoB quantities, at 8 h from LPS administration, without any modification in apoB transcript level. The increment in VLDL-TG is of greater magnitude (8 fold), indicating that during the first phase of the septic response TG-rich VLDL particles accumulate in the circulation (Bartolome et al., 2010).

Different mechanisms seem to be involved in the second phase of septic response. The serum fatty levels drop below controls, which would suggest a lower availability of fatty acids of extrahepatic origin for hepatic VLDL-TG secretion.

Endotoxic rats showed a higher number (10 fold) of circulating VLDL particles in rats at 18 h, but the content of the lipid in each VLDL is reduced (Aspichueta et al., 2006; Bartolome et al., 2010). This was accompanied by high levels of *apob* gene transcript, which could provide for high apoB availability increasing the secretion of lipid poor VLDL particles. Using intact rats in the fasted state, injected with the LPL inhibitor Triton WR-1339, we have shown that the TG and cholesterol secreted into VLDL released by the liver to the blood in 2 h was not enhanced by LPS administration to the same extent as the VLDL-apoB production was (Aspichueta et al., 2005). In this way, hepatocytes isolated from 18 hour LPS-treated rats secreted TG-poor VLDL, and although secretion was highly stimulated, global triglyceride secretion in VLDL remained unchanged. This was related to unchanged rates of fatty acid esterification, measured as [³H]oleate incorporation into TG (Aspichueta et al., 2005; Aspichueta et al., 2006).

In septic hypertriglyceridemic rats, 24 h after sepsis induction, the increase in plasma TG was associated to a decrease in VLDL-TG clearance rate, due to suppressed mRNA levels, protein mass and activity of LPL in peripheral tissues (Lanza-Jacoby et al., 1997; Lanza-Jacoby & Tabares, 1990). Thus, in the early phase of the septic reaction hypertriglyceridemia is mostly due to high VLDL secretion driven by availability of lipids in the hepatocyte; and during the second phase, hypertriglyceridemia would be the result of LPL inhibition, and the increase in apoB transcription would be responsible for the increased secretion of VLDL particles (Fig.3).

4. Zonation of VLDL secretion during sepsis

It has been suggested that parenchymal capacity for VLDL secretion is zoned. Zonation refers to a phenotypic heterogeneity that is well established in many essential liver functions (Jungermann & Katz, 1989). While some authors suggested that VLDL secretion might be higher in perivenous (PV) hepatocytes because of their higher capacity for fatty acid synthesis (Guzman & Castro, 1989), others proposed that it could be concentrated in the periportal (PP) area (Kang & Davis, 2000) since higher expression of the cholesterol synthesis rate-limiting enzyme 3-hydroxy-3-methylglutaryl-CoA reductase was found (Singer et al., 1984).

Zonation has also been evidenced in non parenchymal liver cells. Kupffer cells are more abundant and larger in the PP than in the PV zone (Bouwens et al., 1992), and expression of IL-6, a key cytokine acting on hepatocytes in response to endotoxin, occur preferentially in the PP region (Fang et al., 1998).

After 18 h of endotoxin treatment, highly pure rat PP and PV hepatocyte subpopulations, assessed by cytometry, were maintained in suspension for 2 h. Endotoxin treatment provoked zonation of VLDL secretion. The induction in VLDL-apoB secretion was markedly higher in PP hepatocytes (~90%) than in PV cells (~38%). In addition, the increase in the VLDL associated lipid, particularly in triglycerides, was lower than the enhance in apoB output, consequently producing changes in VLDL features which were triglyceride poor (Aspichueta et al., 2005). Endotoxin doubled apoB mRNA and increased by 50% MTP mRNA in PP hepatocytes when compared to their fasted controls, the increase in apoB

genetic expression was of a lesser extend in PV cells. Regarding to de novo synthesis of lipids for VLDL assembly, the incorporation of [³H]acetate into TG and cholesterol did not change by endotoxin challenge.

We concluded that periportal and perivenous hepatocytes exhibited similar capabilities for VLDL assembly and secretion in normal conditions; and, only the endotoxic condition led PP hepatocytes to a marked increase in TG-poor VLDL secretion (Fig 4).

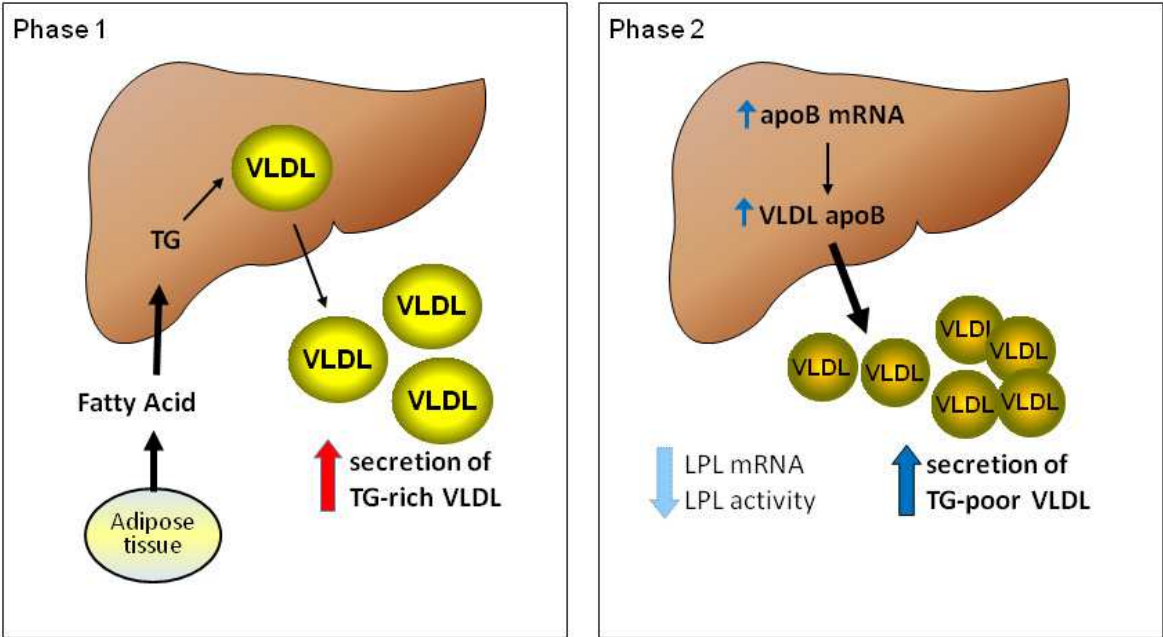


Fig. 3. Proposed model for the biphasic response to endotoxin in VLDL metabolism. In the first phase the stimulation of lipolysis provides fatty acids that are taken by the liver and esterified to be secreted into TG-rich VLDL. In the second phase apoB mRNA levels are increased providing the apolipoprotein for secretion of TG-poor VLDL.

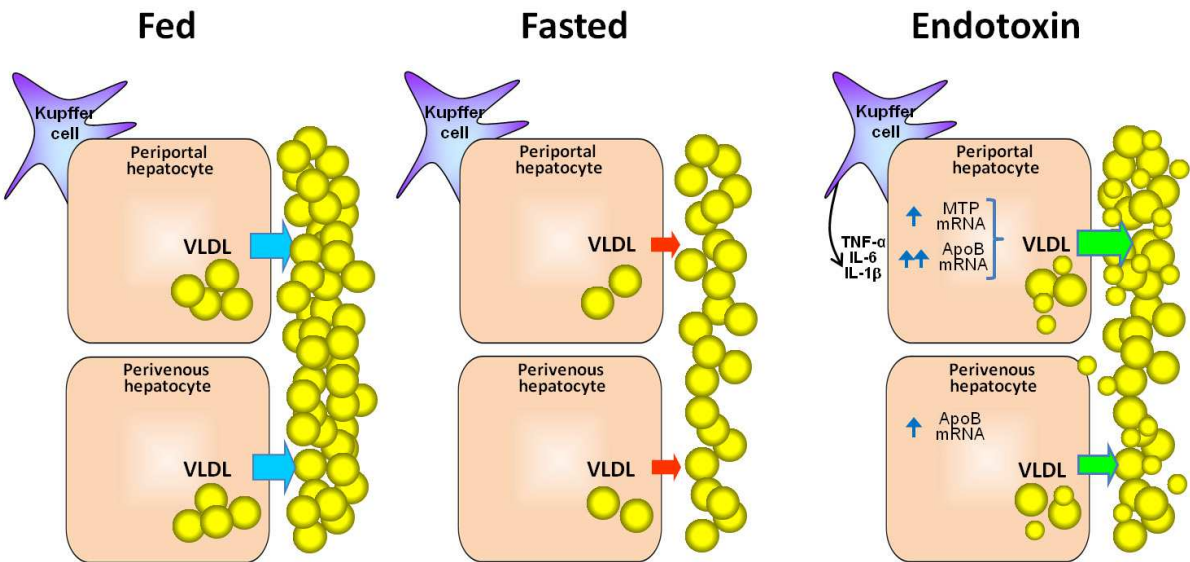


Fig. 4. Model of VLDL secretion by periportal and perivenous hepatocytes in fed state and 18 h after fasting or endotoxin treatment. Endotoxin effect when compared with the fasted state is marked with ➡

5. Kupffer cell mediators and VLDL secretion

During the acute phase of the septic response, Kupffer cells, the resident macrophages in the liver, release a plethora of soluble bioactive molecules, among them soluble pro-inflammatory mediators as cytokines, particularly TNF- α , IL-6 and IL-1 β . These cytokines would act locally on nearby hepatocytes as paracrine factors promoting VLDL secretion and many other metabolic changes that accompany the inflammatory reaction.

We confirmed a rapid release of TNF- α and IL-6 into the bloodstream in rats after 2 h of LPS injection (1 mg/Kg bw), whereas the IL-1 β maximum level was observed at 6 h and the rise was less accentuated. Basal levels were recovered in all cases at 12 h from the LPS treatment (Bartolome et al., 2008).

Administration of cytokines to animals has been shown to mimic the sepsis induced alterations in lipid metabolism. TNF- α , IL-6 and IL-1 β administered to rodents induce triglyceride synthesis and promote rises in VLDL-TG (Khovidhunkit et al., 2004). In the case of TNF- α and IL-6 administration, the hypertriglyceridemia has been reported to be secondary to higher lipolysis in peripheral tissues; consequently more fatty acids in blood are available and can be recruited by liver. In some studies, the three cytokines have been shown to stimulate hepatic de novo fatty acid synthesis (Feingold et al., 1989) and TG secretion (Feingold et al., 1991; Nonogaki et al., 1995), and decrease adipose tissue LPL activity (Feingold et al., 1994; Popa et al., 2007). Nevertheless, the reduction in LPL was delayed several hours with respect to hypertriglyceridemia (Esteve et al., 2005; Popa et al., 2007) and blockade of TNF- α or IL-6 function in septic mice inhibited hypertriglyceridemia without affecting LPL activity (Feingold et al., 1994).

In order to address the role of Kupffer cells in VLDL oversecretion during endotoxemia, we analyzed the response of rat primary hepatocytes to the direct effect of LPS-stimulated KC or unstimulated products. Hepatocytes were cultured for 8 h with the conditioned medium containing the mediators generated in 16 h by Kupffer cells after a previous 4 h culture with or without LPS. The exposure of hepatocytes to unstimulated KC conditioned medium resulted in doubled the secretion VLDL particles of normal composition. Cells cultured in LPS stimulated KC medium secreted further more VLDL particles that were enriched in PL (Bartolome et al., 2008). Regarding to apoB expression, KC products multiplied by two the abundance of apoB mRNA and no further increment was caused by specific LPS-triggered products. In any case was MTP mRNA modified. The high PL available would protect apoB from degradation, explaining the increase in apoB secretion in cells challenged by LPS-KC medium.

There are few studies investigating the direct effect of cytokines on VLDL secretion, and contradictory results have been reported using different cell types. In HepG2 cells IL-6 and IL-1 β were found to reduce apoB secretion although apoB mRNA levels were increased (Yokoyama et al., 1998). However, in IL-6 treated murine hepatocytes, enhanced apoB synthesis, which corresponded with high apoB mRNA levels, was found to be the primary mechanism for increased lipoprotein secretion (Sparks et al., 2010). They also found that IL-6 did not alter the decay rate of apoB mRNA transcripts, concluding that it favours secretion of apoB-containing lipoproteins by increasing availability of apoB through changes in *apob* gene transcription (Sparks et al., 2010).

Our studies in rat hepatocyte cultures, have demonstrated that the inflammatory cytokines TNF- α , IL-6 and IL-1 β , over a wide range of concentrations, enhanced VLDL-apoB secretion linked to upregulation of apoB mRNA expression (Bartolome et al., 2007; Bartolome et al.,

2008; Perez et al., 2006). IL-1 β was the most potent and was the only one presenting a dose-response effect. The effect of the three cytokines was redundant, as the increase was not additive when they were combined. However, none of the treatments with cytokines modified the amount of TG and total lipids secreted as components of VLDL, suggesting that these particles are lipid poor.

We conclude that Kupffer cells play a role in the rise of VLDL secretion detected during the inflammatory processes and that the three cytokines TNF- α , IL-6 and IL-1 β may be involved, nevertheless other Kupffer cells mediators are necessary to accomplish increased lipid association.

6. Higher apoB availability within the hepatocytes

As stated before, the assembly of VLDL is a complex process that depends on the availability of lipids and apoB (Davidson & Shelness, 2000).

Since we have found that under LPS treatment VLDL-apoB secretion was always increased, and given that not always enhanced apoB secretion is linked to high levels of apoB transcript, we hypothesized that during the acute phase response, transcriptional or post-transcriptional regulation affecting apoB mRNA levels might occur supplying more apoB for VLDL assembly.

During the first phase of the septic response we detected elevated circulating VLDL-apoB and -TG after 8 h of LPS treatment without altered apoB transcript levels. Taking into account that at this time point of the septic response, circulating fatty acid levels were elevated, we propose that fatty acid uptake by the liver is increased and large amounts of TG are synthesized. Since the N-terminus of apoB acquires neutral lipids in the endoplasmic reticulum membrane (Hussain et al., 2008), more nucleation sites are expected to be generated in apoB leading to increased apoB secretion. This could result in an increased hepatic secretion of triglycerides in VLDL particles, which would accumulate in the circulation, even in the absence of augmented levels of hepatic apoB mRNA (Bartolome et al., 2010).

In the second phase of the septic response, after 18 h of LPS challenge, enhanced VLDL-apoB secretion is accompanied by increased apoB mRNA levels (Bartolome et al., 2010). In addition, hepatocytes isolated 18 h after LPS administration presented higher levels of apoB transcript and secreted more VLDL particles, been this effect more marked in PP cells. At this time point of the septic response, lipid poor VLDL particles are secreted (Aspichueta et al., 2005) and lipid synthesis is not modified (Aspichueta et al., 2006). Therefore, the increase in *apob* gene transcript would provide the additional apoB necessary to enhance VLDL-apoB secretion. Similarly, the inflammatory cytokines TNF- α (Bartolome et al., 2007), IL1- β (Bartolome et al., 2010) and IL-6 (Perez et al., 2006) augmented the levels of apoB mRNA and secretion of VLDL particles without changing the amounts of lipid secreted in the VLDL.

Our hypothesis was that endotoxin-enhanced VLDL-apoB secretion was driven by higher transcription rates. However, we did not find a rise in transcription rate of *apob* gene when we measured the incorporation of 5'-[α -³²P]-UTP into newly synthesized RNA in liver nuclei from 16 h LPS-treated rats (Bartolome et al., 2010). We reported that global transcription rate in endotoxic liver was nearly two times higher than in control rats as expected in the acute phase response for up-regulating the positive proteins. However, the transcription rate of

apoB gene was unaffected after 16 h of LPS challenge in the treated animals. It cannot be discarded that transcriptional activation may occur transiently during other stages of the APR.

Another aspect involved in regulating mRNA level is the modulation of mRNA stability through regulatory elements residing in the 3'- and 5'-untranslated region (UTR) and adequate RNA binding proteins. HuR is an important protein in stabilizing inflammatory AU-rich elements (ARE)-bearing RNAs. Human apoB mRNA has been reported to contain ARE sequences at 3'-UTRs and bioinformatic analysis of rat apoB transcript revealed the presence of AU-rich regions. Our results demonstrated the specific binding of stabilizing HuR protein to the rat apoB mRNA, although there were no superior binding in livers from LPS treated rats. Consequently, in our conditions it is not likely that apoB mRNA half-life was extended by HuR binding, but we can not discard a role for other stabilizing proteins or changes in the mRNA degradation pathway, but further analysis is need (Fig 5).

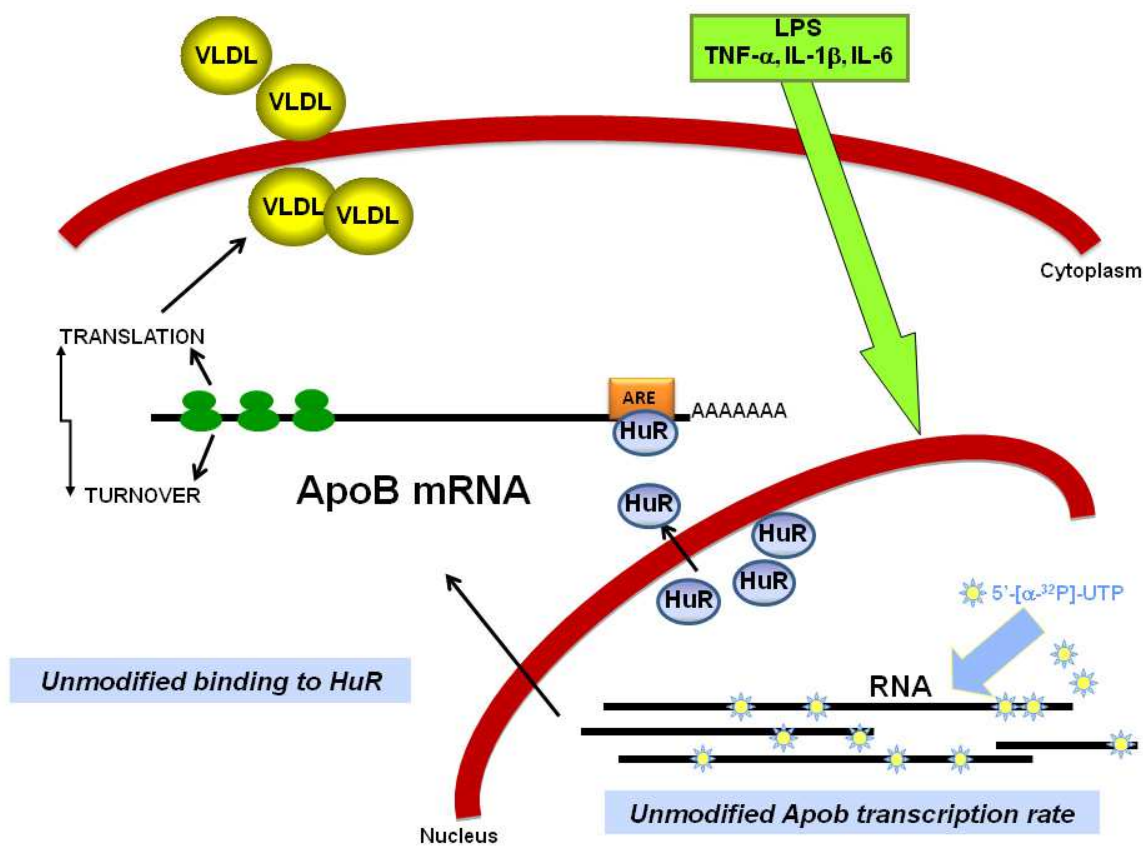


Fig. 5. Endotoxin induce increase in apoB mRNA without altering transcription rate or HuR protein binding.

7. Conclusion

During the septic response, altered VLDL metabolism is responsible for the lipemia of sepsis. Entotoxin promoted changes are biphasic. In the early stage hypertriglyceridemia is accompanied by increased circulating fatty acids levels and a rise in large TG-rich VLDL, whereas the later stage is characterized by high levels of hepatic apoB transcript and TG-

poor VLDL accumulation. In the later stage, the endotoxin induced VLDL secretion is more accentuated in periportal cells. Kupffer cells released products directly promote VLDL assembly and secretion and increase apoB mRNA levels, among these products the cytokines TNF- α , IL-6 and IL-1 β and other mediator/s could play a role in the enhancement of VLD secretion.

8. Acknowledgments

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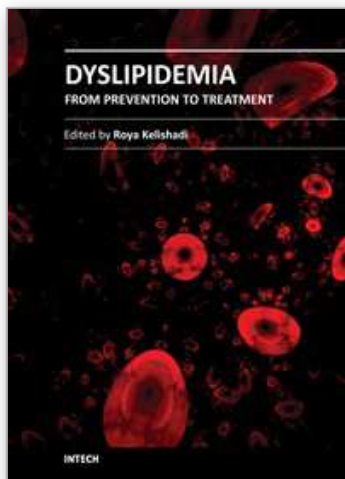
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Dyslipidemia has a complex pathophysiology consisting of various genetic, lifestyle, and environmental factors. It has many adverse health impacts, notably in the development of chronic non-communicable diseases. Significant ethnic differences exist due to the prevalence and types of lipid disorders. While elevated serum total- and LDL-cholesterol are the main concern in Western populations, in other countries hypertriglyceridemia and low HDL-cholesterol are more prevalent. The latter types of lipid disorders are considered as components of the metabolic syndrome. The escalating trend of obesity, as well as changes in lifestyle and environmental factors will make dyslipidemia a global medical and public health threat, not only for adults but for the pediatric age group as well. Several experimental and clinical studies are still being conducted regarding the underlying mechanisms and treatment of dyslipidemia. The current book is providing a general overview of dyslipidemia from diverse aspects of pathophysiology, ethnic differences, prevention, health hazards, and treatment.

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