Introduction
Infection induces dramatic alterations in plasma levels of a large number of proteins. Certain proteins are increased (positive acute phase proteins) while others are decreased (negative acute phase proteins). Alterations in the hepatic production of these proteins are primarily responsible for these changes but regulation also occurs in extrahepatic tissues. Changes in plasma protein levels are believed to play a beneficial role in the host response to infection.

Endotoxin administration mimics many of the changes in protein synthesis that are associated with infection. Infection and endotoxin also lead to profound alterations in serum lipid levels which are now thought to also be part of the acute phase response. The mechanisms that account for these changes and their potential beneficial effects will be discussed.

Effects of endotoxin on triacylglycerols
Endotoxin rapidly increases serum triacylglycerol levels (<2 h) (reviewed in [1]) [2-8], an effect that is sustained for at least 24 h after a single dose of endotoxin [4,7]. The increased triacylglycerol levels are accounted for by an increase in very-low-density lipoproteins (VLDL) [2,7]. The VLDL particles are relatively normal in composition [9,10], although they may have decreased apolipoprotein (apo) E and increased apolipoprotein serum amyloid A (apo SAA) [11,12].

Low doses of endotoxin (0.1-3 \( \mu \)g/100 g body weight; 1/5000–1/1667 of LD50 for rodents) increase serum triacylglycerols primarily by stimulating hepatic triacylglycerol production and VLDL secretion [4,8]. Increased hepatic fatty acid synthesis [4,6,8] as well as increased adipose tissue lipolysis (reviewed in [13]) [4,8] provide fatty acids for the increased triacylglycerol production. Inhibition of endotoxin-induced lipolysis markedly inhibits the increase in serum triacylglycerols, suggesting that the fatty acids are primarily provided by lipolysis [4].

Higher doses of endotoxin (50 \( \mu \)g/100 g body weight; still <1/100 of LD50 for rodents) induce hypertriglyceridaemia by a different mechanism as they do not stimulate hepatic VLDL secretion [4]. Instead, they inhibit the clearance of triacylglycerol-rich lipoproteins, an alteration which has been attributed to a decrease in lipoprotein lipase (LPL) activity in post-heparin plasma and various tissues (heart, adipose and muscle) (reviewed in [13]) [2,4,7]. Other factors, such as decreased apo E content of VLDL [11,12] and decreased macrophage expression of low-density lipoprotein (LDL) receptor-related protein [14], may contribute to the decrease in lipoprotein clearance.

Cytokines [tumour necrosis factor (TNF), interleukin-1 (IL-1) and interleukin-6 (IL-6)] are key mediators of the acute phase response.

Abbreviations used: apo, apolipoprotein; CETP, cholesteryl ester transfer protein; HDL, high-density lipoprotein; HL, hepatic lipase; HMG CoA, hydroxymethylglutaryl coenzyme A; IL, interleukin; LCAT, lecithin:cholesterol acyltransferase; LDL, low-density lipoprotein; LPL, lipoprotein lipase; SAA, serum amyloid A; TNF, tumour necrosis factor; VLDL, very-low-density lipoprotein
and are responsible for the altered synthesis of the acute phase proteins. These cytokines may also mediate the endotoxin-induced alterations in lipid metabolism as they mimic many of the effects of endotoxin. Cytokines induce hypertriglyceridaemia, stimulate hepatic fatty acid synthesis, induce lipolysis and increase VLDL production (reviewed in [1]) [15]. Furthermore, a number of cytokines inhibit LPL activity (reviewed in [1,13]) [16]. The importance of cytokines in endotoxin-induced alterations in lipid metabolism is further demonstrated in endotoxin-resistant mice (C3H/He) which do not produce TNF, IL-1 or IL-6 in response to endotoxin. Endotoxin administration to C3H/He mice does not lead to hypertriglyceridaemia, increased hepatic lipogenesis or decreased LPL activity (reviewed in [13]) [5,6,16]. In addition, pretreatment of mice with TNF antibody blocks the induction of serum triacylglycerols and hepatic fatty acid synthesis, demonstrating the importance of TNF in mediating endotoxin-induced hypertriglyceridaemia [6]. In contrast, pretreatment with IL-1 receptor antagonist or IL-6 antibody does not block the effect of endotoxin on serum triacylglycerol levels, suggesting that neither IL-1 nor IL-6 mediates these effects [6,17]. In rats, neither TNF antibody nor IL-1 receptor antagonist block the endotoxin-induced hypertriglyceridaemia. However, in rats, catecholamines, via α-adrenergic receptors, may mediate the increased hepatic triacylglycerol secretion induced by low-dose endotoxin as well as the decrease in LPL activity induced by high-dose endotoxin [18].

**Effects of endotoxin on cholesterol**

In humans and other primates, infection and endotoxin decrease serum cholesterol, while in non-primates such as rodents, rabbits and dogs, endotoxin increases serum cholesterol levels (reviewed in [1,19]) [2,3,6,9,20].

In rodents the increase in serum cholesterol is delayed in onset compared with the increase in serum triacylglycerols and is primarily due to an increase in LDL cholesterol [9,20,21]. In Syrian hamsters there is an increase in free cholesterol with only a modest increase in esterified cholesterol [22]. Endotoxin increases hepatic cholesterol synthesis and the activity of hydroxymethylglutaryl coenzyme A (HMG CoA) reductase, the rate-limiting enzyme in cholesterol synthesis [6,9]. Increased transcription of HMG CoA reductase leads to increased mRNA and protein levels which are responsible for the increase in enzyme activity [9,23]. The effect of endotoxin on hepatic HMG CoA reductase mRNA is specific, as mRNA levels of other proteins important in cholesterol metabolism, such as HMG CoA synthase and farnesyl pyrophosphate synthase, are not affected [23]. Cholesterol availability for lipoprotein production may also be secured by decreasing the conversion of cholesterol into bile acids. In fact, the activity and mRNA levels of the key enzyme in this process, cholesterol 7α-hydroxylase, are inhibited by endotoxin (Feingold, K. R., unpublished work). In contrast, endotoxin has minimal or no effects on LDL receptor protein or mRNA levels in the liver, the organ primarily responsible for LDL clearance [9,23]. Therefore, increased production of lipoproteins rather than decreased clearance is likely to account for the increase in LDL cholesterol levels.

TNF and IL-1 may be important mediators of the effects of endotoxin on cholesterol metabolism. Both TNF and IL-1 increase serum cholesterol, hepatic cholesterol synthesis and HMG CoA reductase mRNA (reviewed in [1]) [24]. In addition, antibodies against TNF markedly diminish the effects of endotoxin on serum cholesterol, hepatic cholesterol synthesis and the activity of HMG-CoA reductase; however, inhibition of IL-1 activity by IL-1 receptor antagonist only has a weak effect [6].

In primates the decrease in serum cholesterol is due to both decreased HDL and LDL cholesterol [2]. The effects of endotoxin on cholesterol metabolism in primates may also be mediated by cytokines, as TNF, but not IL-1, decreases serum cholesterol (reviewed in [1]). Studies in vitro using Hep G2 cells, a transformed liver cell-line, suggest that decreased cholesterol secretion as well as increased LDL receptor activity may be responsible for the decreased serum cholesterol in primates (reviewed in [1]).

**Effects of endotoxin on high-density lipoprotein (HDL)**

Endotoxin decreases HDL cholesterol levels in both primates and non-primates [2,9,20,22]. This decrease is both rapid (3–4 h) and sustained (24 h) [20,22]. A decrease in cholesterol ester is responsible for the decreased HDL cholesterol as endotoxin increases free cholesterol [3,22]. In some but not all studies, apo A-I levels are decreased [2,9,10,12,25]. In contrast,
endotoxin increases apo SAA from baseline levels of less than 1% to greater than 20% of HDL protein content [25]. In addition, the apo J content of HDL is increased about 5-fold [26]. HDL may also become enriched in apo E [2].

These compositional changes may lead to important alterations in HDL function. Decreased apo A-I on HDL could decrease cellular cholesterol efflux as apo A-I is the major ligand for HDL cell interactions. The endotoxin-induced decrease in extrahepatic expression of apo E that we have recently observed (Hardardóttir, I., unpublished work) may also serve to decrease cholesterol efflux from peripheral cells as extrahepatically secreted apo E may associate with HDL and serve as a ligand for HDL-mediated cellular cholesterol efflux. The increase in SAA and apo J on HDL may be important both for regulating HDL cholesterol levels and HDL function. SAA-rich HDLs are rapidly cleared from plasma [27] and thus increased SAA could contribute to the endotoxin-induced decrease in HDL cholesterol levels. Additionally, SAA is a cholesterol-binding protein that promotes cellular uptake of cholesterol [28], and SAA-rich HDLs have a lower affinity for hepatocytes and increased affinity for macrophages [29]. HDL cholesterol may thus be preferentially directed to macrophages during the acute phase response. Apo J may play a similar role as it has been proposed to be involved in uptake, mobilization and redistribution of lipids [30].

Metabolism of HDL is also dependent on several key enzymes, the activities of which are modified by endotoxin and cytokines. Endotoxin decreases the activity of lecithin:cholesterol acyltransferase (LCAT), which is responsible for esterifying free cholesterol in HDL. Endotoxin decreases hepatic LCAT mRNA levels which accounts for the decrease in plasma LCAT activity and protein [2,3,22]. The decrease in LCAT activity leads to an increase in free cholesterol and a decrease in esterified cholesterol in HDL [3,22]. Esterification of cholesterol is necessary for HDL to accumulate more cholesterol and decreased LCAT activity may therefore contribute to both the decrease in HDL cholesterol levels and a decrease in cholesterol efflux from cells.

Cholesteryl ester transfer protein (CETP), which mediates the exchange of HDL cholesteryl ester for VLDL triacylglycerols, is also affected by endotoxin. In mice overexpressing the human CETP gene in the liver, administration of endotoxin decreases hepatic expression and activity of CETP [31]. In addition, we have recently demonstrated that in hamsters, which have very low hepatic levels of mRNA for CETP, endotoxin decreases mRNA levels for CETP in a number of extrahepatic tissues (Hardardóttir, I., unpublished work). The endotoxin-induced decrease in CETP activity may prevent the transfer of cholesteryl esters from HDL to VLDL, which otherwise would be exchanged freely for the abundant triacylglycerols in VLDL. Decreased CETP activity may thus maintain HDL cholesterol levels under conditions where HDL cholesterol would otherwise be decreased considerably. Maintaining HDL cholesterol levels may be important because of the ability of HDL to prevent the toxic effects of endotoxin (see below).

Endotoxin and infection also decrease the activity of hepatic lipase (HL) [10,32–34]. mRNA levels for HL are not affected during infection, indicating that the decrease in HL activity occurs at the translational or post-translational level [34]. HL is responsible for metabolizing triacylglycerol-rich HDL into remnant HDL2 and pre-β-HDL. The remnant HDL2 is degraded and cleared by the liver, thus decreased HL activity may block clearance and thereby maintain HDL cholesterol levels. Pre-β-HDLs are believed to play a key role in mediating the transfer of free cholesterol from cell membranes. Decreased HL may lead to a reduction in pre-β-HDL levels and thus prevent cholesterol efflux maintaining cholesterol in peripheral cells.

Thus, the endotoxin-induced changes in composition of HDL and the activities of enzymes involved in HDL metabolism may have the following effects (Figure 1): (i) decreasing efflux of cholesterol from peripheral cells to HDL by decreasing apo A-I in HDL, extrahepatic apo E and the activities of LCAT and HL; (ii) maintaining HDL cholesterol levels while decreasing cholesterol efflux from cells by decreasing CETP and HL activity; (iii) redirecting HDL cholesterol away from liver and to macrophages by increasing SAA and apo J on HDL and decreasing HL activity.

**Beneficial effects of the endotoxin-induced alterations in lipid and lipoprotein metabolism**

The alterations in lipid metabolism that occur during infection may be beneficial through a number of different mechanisms: (i) redistribution of nutrients to cells that are important in
host defence, (ii) binding endotoxin and other biological agents and preventing their toxic effects, (iii) competing with viruses for cellular receptors, (iv) binding and targeting parasites for destruction, (v) apolipoproteins neutralizing viruses and (vi) apolipoproteins lysing parasites.

**Redistribution of nutrients**

The elevated serum triacylglycerol levels that accompany infection may provide increased fuel for the elevated metabolic needs that occur during infection (reviewed in [11, 35]). Macrophages, which may have increased energy needs during infection, have an enhanced uptake of triacylglycerol-rich lipoproteins when incubated with endotoxin [36]. Moreover, the distribution of triacylglycerol uptake between tissues may be altered by changes in LPL activity. LPL activity is decreased to a greater extent in adipose tissue than in quadriceps or cardiac muscle, possibly diverting lipids from being stored in adipose tissue to tissues that need energy [16]. Additionally, apo SAA may redirect HDL away from the liver and to peripheral tissues [29] delivering cholesterol to cells involved in the immune response and tissue repair [28]. Finally, the decrease in apo A-I on HDL and the decrease in extrahepatic expression of apo E may play a role in preventing efflux of cholesterol from peripheral cells which may need cholesterol for repair and regeneration of damaged membranes.

**Binding endotoxin and other biological agents and preventing their toxic effects**

All lipoprotein classes have the ability to bind and inactivate endotoxin (reviewed in [19,35]). Serum factors are required for the binding and inactivation of endotoxin. Lipopolysaccharide-binding protein may be one of these serum factors as it catalytically transfers endotoxin to HDL and is required for binding and neutralization of endotoxin by HDL [37]. Toxicity of endotoxin is to a large extent mediated by activation of monocytes/macrophages and subsequent release of cytokines such as TNF and IL-1. Endotoxin binding to lipoproteins inhibits specific endotoxin–macrophage interactions [38] and prevents endotoxin-induced cytokine release (reviewed in [1,19,35]) [39,40].

*In vivo*, all lipoprotein classes (chylomicrons, VLDL, LDL and HDL) protect mice against endotoxin-induced death when incubated with endotoxin before its administration [41]. Triacylglycerol-rich lipoproteins also protect animals from death induced by abdominal sepsis [42]. The endotoxin-induced lethality can also be prevented by infusing chylomicrons into rats up to 30 min after a lethal dose of endotoxin [43]. Chylomicrons enhance plasma clearance and hepatic uptake of endotoxin, with endotoxin being shunted preferentially to hepatocytes and away from hepatic macrophages, thereby increasing endotoxin excretion in bile [44]. Increased
survival correlates with a reduction in peak serum levels of TNF, providing a possible mechanism by which lipoproteins protect against endotoxin-induced death [45].

Increasing serum HDL by making mice overexpress human apo A-I leads to lower serum cytokine levels and improved survival [46]. The physiological significance of lipoproteins in protecting from endotoxin-induced lethality is further demonstrated in animals rendered hyperlipidaemic either by administration of 4-aminopyrrolo[3,4-H]pyrimidine, which prevents hepatic secretion of lipoproteins, or by administration of oestradiol, which increases the number of hepatic LDL receptors, leading to increased lipoprotein clearance. Both treatments markedly increase sensitivity to endotoxin-induced mortality, and administration of exogenous lipoproteins, which increases levels of serum lipids into the physiological range, reduces the increased mortality [47].

In addition to binding and inactivating endotoxin, lipoproteins also bind viruses and inhibit their replication and infectivity (reviewed in [19]) [48–50]. Furthermore, lipoproteins bind urate crystals and prevent their inflammatory effects (reviewed in [1]). Lipoproteins may thus represent a non-specific defence mechanism in the host response to infection.

**Competing with viruses for cellular receptors**

Certain viruses use the LDL receptor for entry into cells [51–54]. LDL may compete with viruses for cellular uptake and the elevated LDL levels during infection may therefore be beneficial.

**Binding and targeting parasites for destruction**

LDL binds to the parasite *Schistosoma mansoni* [55]. The LDL becomes oxidized and targets the parasite to the scavenger receptor on macrophages. The oxidized LDL is removed by the scavenger receptor, leaving the parasite exposed to direct attack by the macrophages which kill the parasite [56].

**Apolipoproteins neutralizing viruses**

Apolipoproteins, especially apo A-I, neutralize several viruses, including HIV probably by inhibiting virus-induced cell fusion and entry of the virus into the host cell [57–59]. Displacement of apo A-I on HDL by apo SAA during infection may serve to provide free apo A-I for this function.

**Apolipoproteins lysing parasites**

HDLs from humans and baboons, which are not susceptible to infection by the parasite *Trypanosoma brucei brucei*, have the ability to lyse this parasite; in contrast, HDLs from species susceptible to infection by this parasite do not [60]. Apo A-I was shown to be the trypanolytic factor of human and baboon HDL [61]. However, more recently, the human haptoglobin-related protein which resides on HDL was demonstrated to be responsible for lysing the parasite [62].

**Summary**

Endotoxin, via cytokines, induces marked changes in lipid metabolism which are now considered part of the acute phase response. The endotoxin-induced hyperlipidaemia may represent a nonspecific immune response that can decrease the toxicity of a variety of harmful biological and chemical agents and serve to redistribute nutrients to cells important in host defense. The endotoxin-induced changes in lipid metabolism may therefore be beneficial.

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