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Carnitine and Fatty Acid Oxidation in Sepsis

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Summary. Fatty acid oxidation is usually thought of as being a preferred *ATP* source during sepsis, as shown by the decrease in respiratory quotient in septic patients and animals. However, fatty acid oxidation may be impaired relative to circulating triglyceride levels, resulting in increased cycling between triglycerides and non-esterified fatty acids. The rate of fatty acid oxidation is critically dependent on the stage of sepsis. Carnitine may be depleted during sepsis by a combination of muscle wasting, erythrocyte haemolysis, decreased tissue uptake, reduced kidney reabsorption of free carnitine, and increased excretion of acyl-carnitines. Whether there may be any beneficial effects of carnitine supplementation during sepsis, is, as yet, uncertain.

Keywords. Fatty acids; Lipids; Oxidations; Carnitine; Sepsis.

Introduction

The role of *L*-carnitine in allowing mitochondrial entry of fatty acids for beta-oxidation is well understood [1], however, whether carnitine metabolism or fatty acid oxidation are altered in critical illness or sepsis are not as well known. Sepsis, the systemic inflammatory response to infection, is a major cause of morbidity and mortality. During sepsis, failure of multiple organs frequently occurs, which may be due to bioenergetic failure [2]. Maintaining cellular *ATP* levels is therefore of primary importance during sepsis. Fatty acid oxidation is an important source of *ATP* for many tissues, particularly when supplies of other nutrients may be compromised. In addition, inhibition of fatty acid oxidation by lack of intracellular carnitine could lead to accumulation of toxic acyl-CoA esters, so that maintenance of adequate carnitine levels during sepsis and inflammation is important. In sepsis, lipid is potentially a useful energy substrate as it is energy-dense so that a high number of calories can be infused in a low volume; many septic patients are restricted in their intravenous fluid intake because of capillary leak and oedema. It is our aim in this article to review the existing knowledge concerning fatty acid oxidation in sepsis, and to understand whether

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alterations in carnitine metabolism and status during sepsis affect fatty acid oxidation.

Physiology of Fatty Acid Oxidation (Fig. 1)

Under fasting conditions, the insulin/glucagon ratio is low which results in the stimulation of lipolysis. Triacylglycerol stores in adipose tissue are hydrolysed to free fatty acids, by the action of hormone-sensitive lipase (HSL), which are then released into the circulation and subsequently taken up and oxidised by most tissues apart from the central nervous system (CNS) and erythrocytes. Usually, there is a strong correlation between circulating NEFA levels and fatty acid oxidation [3]. However, not all NEFA are oxidised and even under normal conditions, about 50% are recycled to triglycerides [4]. Circulating triglycerides can be converted to NEFA by the action of lipoprotein lipase and taken up by tissues. In liver, under these conditions, fatty acids are broken down to acetyl-CoA which is used almost exclusively for the formation of ketone bodies (acetoacetate and *D*-3-hydroxybutyrate). Ketone bodies are, in turn, exported for oxidation by extra-hepatic tissues. Amino acids released from skeletal muscle can be utilised by the liver for gluconeogenesis (*e.g.*, alanine) or ketogenesis (branched chain amino acids). Simultaneously, glycogenolysis occurs and in liver, and to a lesser extent kidney, glucose is mobilised for extra-hepatic utilisation. Skeletal muscle also has

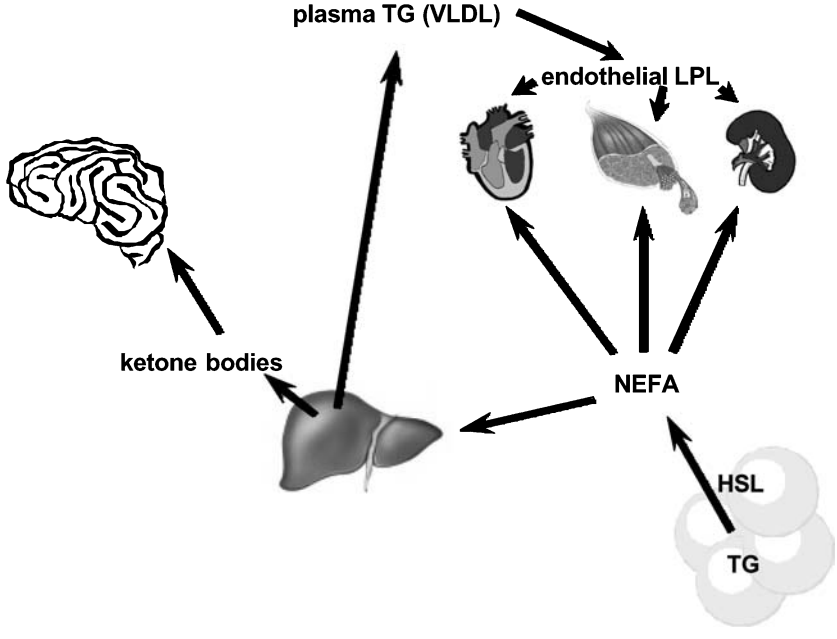

Fig. 1. *Physiology of fatty acid metabolism:* Fatty acids (non-esterified fatty acids, NEFA) are released from adipose tissue triacylglycerol stores (TG) by the action of hormone-sensitive lipase (HSL); NEFA can be taken up and oxidised to CO_2, yielding *ATP*, by heart, muscle, and kidney, and oxidised to ketone bodies or re-esterified to circulating TG very-low density lipoprotein (VLDL) by the liver; ketone bodies are oxidised by the brain, which cannot oxidise fatty acids directly; endothelial lipoprotein lipase (LPL) releases NEFA from circulating TG, which are then taken up and oxidised

substantial glycogen reserves, but these are utilised endogenously particularly during exercise. Thus the net affect of fasting or indeed any stress leading to counter-regulation of insulin, is a switch from a fuel economy based on carbohydrate to one in which a greater proportion of energy is derived from the oxidation of lipid. The resultant sparing of glucose allows the direction of glucose to those tissues with an obligatory requirement such as CNS. The heart under most conditions obtains much of its *ATP* requirement from fatty acid oxidation [5].

Lipolysis and Free Fatty Acid Metabolism in Sepsis

Studies in adults have shown that the metabolic response to trauma and sepsis is characterised by hypermetabolism and increased tissue catabolism [6, 7]. During sepsis, fat is usually thought of as being a preferred fuel for oxidation [8–11]. Lipolysis is increased in response to stimulation by catecholamines, resulting in an increase in rate of appearance of both glycerol and free fatty acids [12], which may be aggravated by the decreased ability of insulin to suppress lipolysis in severe sepsis [13]. During sepsis and critical illness, however, recycling of NEFA to triglycerides is greatly increased [14, 11], resulting in elevated concentrations of triglycerides [15]. This results in variability in NEFA concentration, which can be decreased, comparable to non-septic patients, or increased [16]. In addition, some studies have suggested inhibition of lipoprotein lipase [17–20], an increase in hepatic re-esterification to VLDL [21], or decreased LDL clearance [22] during sepsis, all of which would lead to increased triglyceride levels. NEFA is usually bound to albumin in plasma, and the availability of NEFA for cellular uptake will be, at least in part, determined by the molar ratio of NEFA to albumin, as different binding sites on albumin have different affinities. During sepsis, hypoalbuminaemia in a common finding that could be due to decreased synthesis or increased capillary leakage. The effects of hypoalbuminaemia during sepsis on availability of NEFA for oxidation are not known, although in a study of nephrotic patients with hypoalbuminaemia, it was shown that there was an increase in albumin affinity for fatty acids, and a wide variation in fatty acid availability [23]. As well as the above factors, there may be a relative inhibition of fatty acid oxidation compared to plasma non-esterified fatty acid and triglyceride levels. This could be due to inhibition of oxidation of non-esterified fatty acids. Different authors have reported fatty acid oxidation to be increased, decreased, or unaltered in sepsis, but these variable findings could be due to variation in species studied, age, stage of sepsis, model of sepsis, methodology, or nutritional state of human patients. We consider these findings below.

Fatty Acid Oxidation in Sepsis

Human Patient Studies

Several studies in adult human patients have shown a lower respiratory quotient in septic patients compared to controls reflecting relatively greater utilisation of fat rather than carbohydrate for oxidation during sepsis [10, 9, 24–26] (respiratory quotient, that is the ratio of oxygen utilised divided by CO_2 evolved, is 0.7 for fat

oxidation and 1.0 for carbohydrate oxidation). Similarly, in study measuring fatty acid turnover with [1,2]^{13}C-palmitate, *Shaw* and *Wolfe* showed that septic patients had enhanced rates of oxidation of both exogenous and endogenous fat, and had enhanced rates of futile recycling of fatty acids [11]. However, other authors have shown, by measurement of arterio-venous differences in metabolites, that there is a decrease in the contribution of free fatty acid utilisation as an energy source for the myocardium in patients with septic shock, with a corresponding increase in lactate utilisation [27, 28]. These apparently conflicting observations can be reconciled when the stage of sepsis is taken into account. In a study of septic adults, *Giovannini et al.* showed that although septic patients had a lower respiratory quotient than non-septic patients (*i.e.*, increased reliance on fat oxidation), when the septic patients were split into two groups depending on the presence of multiple organ failure with impaired oxygen extraction, it was found that the more severely septic patients had a respiratory quotient of 1.23, suggestive of net lipogenesis and impaired fatty acid oxidation [29]. In premature septic neonates, *Park* and co-workers found that oxidation of ^{13}C-triolein was impaired and that infusion of parenteral lipids led to a greater increase in both triglycerides and free fatty acids than control patients [30, 31]. Infused lipid was oxidised similarly by septic and non-septic adults [32], and we found similar results in infants and children with sepsis (*Caresta*, *Pierro*, *Peters*, and *Eaton*, unpublished), although some patients with meningococcal disease showed no drop in respiratory quotient with lipid infusion. Studies of ketone body turnover during sepsis in adults has shown that at normal NEFA concentrations, ketogenesis is comparable to control patients, but that septic patients are not able to raise their ketogenic rate in response to an increase in NEFA levels [33].

Animal Model Studies

Several different animal models of sepsis are used, and there is variability in response between the models. The three most commonly used models are: endotoxaemia induced by administration of lipopolysaccharide, caecal ligation and puncture (and/or implantation of faecal material), and administration of live bacteria. Indirect calorimetry studies have, in animals, shown opposite results to those observed in humans: adult rats made septic by either endotoxaemia or caecal ligation and puncture showed impaired lipid oxidation [34] and in suckling endotoxaemic rats, we showed that there is an increase in respiratory quotient, reflecting decreased lipid utilisation [35]. In the same suckling rat model of endotoxaemia, we have also shown inhibition of hepatocyte oxygen consumption from fatty acid substrates [36]. In a caecal ligation and puncture model using adult rats, *Fried et al.* showed similar results to those of *Giovannini et al.* in humans, *i.e.*, that oxidation of exogenous lipid was impaired in more severely septic animals [37]. Other groups have shown inhibition of hepatic ketogenesis in endotoxic rats [38], decreased hepatic ketogenesis in bacterially infected rats [39–41], and decreased oxidation of octanoyl-carnitine by heart and muscle from endotoxic rabbits [42]. In dogs with endotoxic shock, fatty acid oxidation was shown to be diminished [43] whereas *Shaw* and *Wolfe* found unaltered ability of dogs given live bacteria to oxidise fatty acids [44]. Other groups have also found normal fatty acid oxidation in heart from rats injected with live bacteria [45] or heart from rats given faecal innoculate [46].

Effects of Sepsis on Individual Enzymes of Fatty Acid Oxidation

Several different studies have examined the effects of sepsis or endotoxaemia on enzymes involved in the oxidation of fatty acids by cells (see Fig. 2 for location of enzymes and proteins discussed). Fatty acid transport protein (FATP) and fatty acid translocase (FAT/CD36), two proteins which may be involved in the transfer of fatty acids across the plasma membrane, are affected by endotoxaemia: in adipose tissue, heart, skeletal muscle, brain, spleen, and kidney, both are down regulated whereas in liver FATP is decreased and FAT/CD36 is increased [47]. Fatty acid binding proteins (FABPs) are responsible for cytosolic trafficking of fatty acids and thus can deliver fatty acids both to the mitochondria for oxidation and to the endoplasmic reticulum for esterification, although their precise roles have not yet been entirely delineated [3]. Liver and heart FABP are both down-regulated by endotoxaemia [48]. Fatty acids must be activated to their CoA esters before being either oxidised or esterified, and the enzymatic activity responsible for this is acyl-CoA synthase. Interestingly, endotoxaemia inhibited acyl-CoA synthase activity in adipose tissue, heart, and muscle and the mitochondrial activity in liver (*i.e.*, the activity responsible for directing fatty acids to oxidation) but increased the activity of the liver microsomal enzyme (*i.e.*, the activity responsible for directing fatty acids towards esterification), thus potentially explaining the increase in hepatic triacylglycerol formation compared to fatty acid oxidation in sepsis [49].

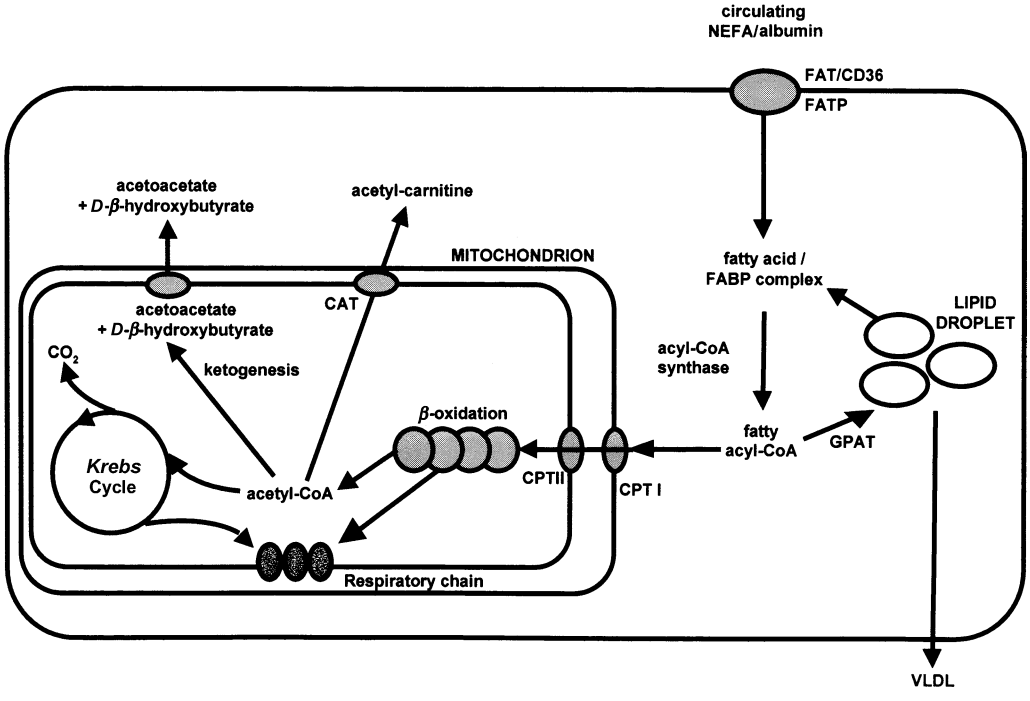

Fig. 2. *Hepatic fatty acid oxidation:* Circulating non-esterified fatty acids (NEFA), bound to albumin, are taken up by cells *via* FAT/CD36 (fatty acid translocase) or FATP (fatty acid transfer protein); fatty acids are bound within the cytosol by fatty acid binding protein (FABP) and can be oxidised in the mitochondria, *via* carnitine palmitoyl transferase I (CPT I), or esterified to triacylglycerol, *via* glycerol-3-phosphate acyl transferase (GPAT)

However, the role of different acyl-CoA synthase isoforms with respect to esterification and oxidation has recently been delineated [50], and the relationship of these individual isoforms to the activities measured in endotoxaemia is uncertain. As well as the potential channelling of acyl groups towards esterification/oxidation by different isoforms of acyl-CoA synthase, the enzymes which control the entry of acyl groups into the mitochondrial β-oxidation spiral (carnitine palmitoyl transferase I, CPT I) or into esterification to triacylglycerol (glycerol-3-phosphate acyl transferase) are thought to be important in controlling the fate of intracellular acyl groups [3, 51] and could therefore be responsible for decreased fatty acid oxidation and increased triacylglycerol synthesis observed in sepsis. *Kiuchi et al.* demonstrated reciprocal regulation of glycerol-3-phosphate acyl transferase (upregulated) and CPT I (downregulated) during sepsis [52], and the diversion of acyl groups towards esterification may be exacerbated by elevated circulating concentrations of glycerol (resulting from accelerated adipose tissue lipolysis) [16] and inhibition of intracellular glycerol oxidation, resulting in elevated intracellular glycerol-3-phosphate levels [53]. Hepatic CPT I activity has been shown to be decreased in parallel with ketogenesis in endotoxic rats [38, 54] and after caecal ligation and puncture [52], whereas other groups have shown either an increase in CPT I activity in a caecal ligation and puncture model [55] or no change in CPT I or CPT II activity following caecal ligation and puncture in weanling or adult rats [56]. In our model of suckling rat endotoxaemia, we showed inhibition of the muscle isoform of CPT I in the heart [57] by tyrosine nitration [58] whereas activity of kidney CPT I (*i.e.*, the liver isoform) was unaltered [57], and the mRNA for muscle CPT I was found to be decreased in mouse heart by endotoxaemia *via* down-regulation of nuclear hormone receptors [20]. Although CPT II activity is not thought to be important in the control of beta-oxidation flux, CPT II activity, protein, and mRNA levels are decreased by peritoneal sepsis [59]. The hepatic enzyme which is thought to be responsible for much of the control of the formation of ketone bodies from acetyl-CoA, hydroxymethylglutaryl-CoA synthase, did not alter in endotoxic animals whose rate of overall ketogenesis was decreased [38]. Peripheral ketone body utilisation may be impaired during sepsis as succinyl-CoA:3-ketoacid CoA transferase is inhibited during endotoxaemia [60], which could explain the inability of *D*-hydroxybutyrate administration to slow leucine oxidation in human sepsis [61]. Mitochondrial fatty acid oxidation is dependent on the integrity of the mitochondrial respiratory chain [62], and many authors have shown impairment of mitochondrial respiratory chain function during sepsis [63, 64], which in turn lead to decreased fatty acid oxidation. This is supported by decreased arterial ketone body ratio, reflecting alterations in mitochondrial redox state [65, 66].

Carnitine Status during Sepsis

Critical illness, such as sepsis, trauma, burns, or surgical trauma, has been shown in several studies, both in humans and in experimental animals, to lead to increased urinary carnitine losses [67–70], and it has been suggested that urinary carnitine excretion is a measure of tissue catabolism [67], although this is not a universal finding [71]. Ninety-eight percent of whole-body carnitine is stored in muscle, and carnitine can be synthesised in the liver and kidneys, and obtained from the diet

[72]. The increased urinary losses of carnitine are therefore likely to be due to the muscle wasting associated with mobilisation of amino acids during sepsis, and this is supported by the finding of decreased carnitine levels in heart and skeletal muscle of suckling septic rats [56], of heart of septic adult rats [71], and skeletal muscle of both humans and dogs with sepsis [73]. In addition, measurement of femoral arterio-venous carnitine differences in critically ill patients has shown a net loss of carnitine from muscle [74]. As muscle cannot synthesise carnitine, uptake *via* a carrier-mediated process is necessary, and *Lanza-Jacoby* and co-workers demonstrated that sepsis leads to a decrease in carrier-mediated transport of carnitine in rat heart [75]. The best characterised plasma membrane carnitine transporter, OCTN2, is responsible for muscle carnitine uptake and so is likely to be the enzyme which is inhibited. The same enzyme is present in kidney [76], where carnitine reabsorption takes place, so a similar inhibition of this enzyme in the kidney could explain the increased carnitine losses during sepsis, and the decreased renal concentration of carnitine observed in endotoxic dogs [77]. However, other carnitine transporters, such as the low-affinity liver transporter [78], have been incompletely characterised [79], and it is not known whether export of carnitine synthesised within the liver is altered during sepsis. The liver content of carnitine has been shown to increase during endotoxaemia [80] and sepsis [69, 81] although this is not a universal finding [56, 82, 54]. Plasma carnitine levels do not necessarily give a reliable indication of whole body carnitine status; plasma carnitine is dependent on many factors, each of which may be altered in sepsis, such as release of carnitine from muscle or haemolysed erythrocytes, impaired carnitine uptake by muscle and heart, and decreased kidney reabsorption of carnitine. Hence, reports of plasma or serum carnitine concentration in sepsis have been somewhat variable: various groups have reported increased [56, 77, 69, 71, 75], decreased [83], or unaltered [70, 84] circulating carnitine concentration. This variability is highlighted by the study of *Mela-Riker et al.*, who showed that plasma carnitine could either be decreased or increased, depending on whether a moderate or severe model of sepsis in rats was used [81]. Carnitine is present in the circulation and in tissues in both free and esterified forms. Short-chain acyl-carnitines usually represent the major part of esterified carnitine, and acetyl-carnitine is the main component of the short-chain acyl-carnitine fraction. Plasma acetyl-carnitine concentration represents a reasonable estimate of whole-body fatty acid oxidation, but acetyl-carnitine can be taken up and used by tissues such as muscle [85]. Other acyl-carnitines, particularly long-chain acyl-carnitines, result from incomplete fatty acid oxidation and can be toxic under some conditions. Excretion of acyl-carnitines can therefore be considered a detoxification process, and indeed much of the increase in carnitine excretion during sepsis can be accounted for as acyl-carnitine [69]. Determination of the individual acyl-carnitine species present in plasma or excreted would be useful, however, to our knowledge their concentrations during sepsis have not been reported.

Effects of Carnitine Administration during Sepsis

Few studies have examined the effect of carnitine or its acyl-derivatives during sepsis: in septic patients acetyl-carnitine administration decreased respiratory quo-

tient, suggesting an enhancement of fatty acid oxidation [70]. In another study, during which septic patients were infused with intravenous triglyceride, with or without carnitine, patients that received carnitine had increased fatty acid oxidation and ketogenesis [86]. In an animal model, administration of carnitine or the γ-hydroxybutyryl ester of isovaleryl-carnitine accelerated recovery from endotoxaemia but did not alter survival, whilst preventing the endotoxin-induced rise in circulating triglycerides [80]. In another study of endotoxaemia in rats, carnitine administration before endotoxin significantly improved survival, but did not affect the hepatic activity of enzymes of fatty acid oxidation, or hepatic levels of ketone bodies [54]. Plasma free carnitine and short-chain acyl carnitine, and hepatic free carnitine, short-chain acyl-carnitine, and long-chain acyl carnitine were significantly increased by carnitine administration [54]. In a rat model of caecal ligation and puncture, carnitine administration prevented the sepsis-induced decrease in branched chain amino acids and glutamine, and the authors speculated that this was due to increased fatty acid oxidation sparing utilisation of these amino acids [87]. However, it should not be concluded that all the effects of carnitine are mediated *via* effects on fatty acid oxidation. Carnitine may additionally have glucocorticoid-like effects; it has recently been shown that carnitine activates glucocorticoid-receptor-α and decreases pro-inflammatory cytokine production [88], which could explain the results of previous studies in which carnitine treatment suppressed endotoxin-induced cytokine production [89–92].

Conclusions

Although lipids are usually thought of as being a preferential fuel during sepsis, fatty acid oxidation may be impaired relative to circulating triglyceride levels, resulting in increased cycling between triglycerides and non-esterified fatty acids. However, the rate of fatty acid oxidation is critically dependent on the stage of sepsis. Carnitine may be depleted during sepsis by a combination of muscle wasting, erythrocyte haemolysis, decreased tissue uptake, reduced kidney reabsorption of free carnitine, and increased excretion of acyl-carnitines. Whether there may be any beneficial effects of carnitine supplementation during sepsis, is, as yet, uncertain.

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