Review

Essential fatty acids (EFA): Role in pancreatic hormone release and concomitant metabolic effect

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Certain fatty acids have been identified as essential fatty acids (EFA) because they cannot be made by mammalian tissues and have to be obtained from plant and marine dietary sources. These fatty acids are the polyunsaturated fatty acids (PUFA), linoleic acid (18:2, ω 6), and linolenic acid (18:3, ω 3). Apart from the fact that they can be elongated and desaturated to yield bioactive molecules with longer chains and higher double bonds such as arachidonic acid (from linoleate) and eicosanoids (from both fatty acids), they are very easily oxidized in the presence of oxygen to provide metabolic energy. Recent studies have also shown that PUFA are potent insulin secretagogues. In this review article, an attempt has been made to evaluate these new data and to discuss their potential usefulness in nutritional support.

Keywords: linoleic acid; linolenic acid; metabolism; insulin; glucagon; parenteral nutrition

Introduction

Since the days of the classical study by Burr and Burr,[1] which first demonstrated a new deficiency disease produced by the rigid exclusion of fat from the diet of experimental rats, it has become clear that certain polyunsaturated fatty acids (PUFA) are essential to life.[2,3] The essential fatty acids (EFA) that have been identified from both animal and human experimental models are linoleic acid (18:2, ω6) and linolenic acid (18:3, ω3), which cannot be synthesized by mammalian tissues but must be obtained in the diet from plant and marine sources.[3,4] Although historically, arachidonic acid (18:4, ω6), was thought to be one of them,[1,5] it is now known that mammals possess a series of desaturases and elongases for metabolism of linoleate to arachidonate.[5,6] The EFA occur in two family series of omega-6 (linoleate) and omega-3 (linolenate), each with numerous metabolically related members,[3,5] although all fatty acids (both essential and nonessential) affect the metabolism, the pattern and proportions of each other in functional lipids of importance.[3,7] A third family of unsaturated fatty acids not classified as essential fatty acids is that of the omega-9 series. Palmitic acid (C16:0) can be elongated to stearic acid (C18:0); this is desaturated to oleic acid (C18:1,ω9), which itself can be the precursor molecule in the diet for the biosynthesis of the omega-9 series. The classification of unsaturated fatty acids into omega-families arises out of a nomenclature system of identifying the position of the first double bond from the methyl (CH_3) end of the fatty acid chain. Thus, in the omega-9 series, the first double bond occurs at the ninth position from the methyl end of the molecule, and the parent fatty acid in this family is oleic acid. Because no member of the omega-9 series is considered an essential fatty acid, this family will not be discussed further in this article. In the omega-6 and omega-3 series, the positions of the first double bonds are at the sixth and third positions, and the parent fatty acids in these two families are linoleic acid and linolenic acid, respectively (*Figure 1*). These omega-families of unsaturated fatty acids are not interconvertible. It is pertinent to point out here that while linoleic acid continues to be accepted as an EFA, the position of linolenic acid as an essential nutrient is controversial.[8] The provision of as little as 1–2% of dietary calories in the form of linoleic acid will support normal growth and development and prevent

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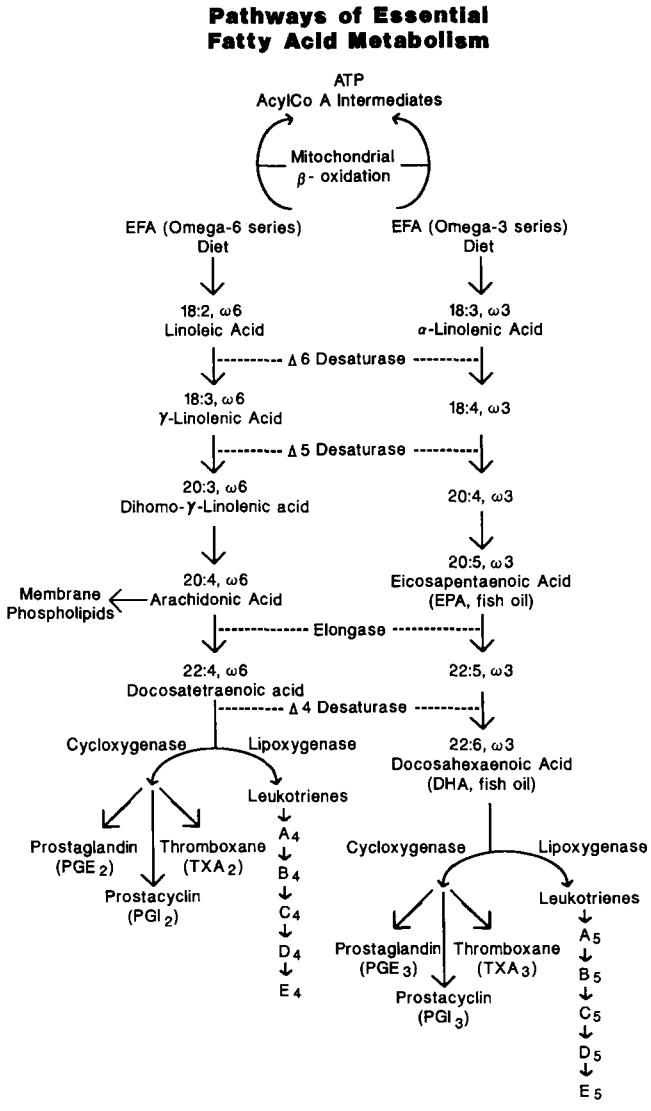

Figure 1 Outline of pathways of essential fatty acid metabolism; the same enzymes catalyze the reactions for each of the omega-6 and omega-3 series.

the clinical symptoms of essential fatty acid deficiency (EFAD),[3,5] and in deficient animal or humans, linoleic acid will reverse all the known clinical manifestations of EFAD.[9-15] However, because other dietary fatty acids compete for the chain-elongating and desaturating enzymes, a level of 3% of energy as essential fatty acids was proposed as a recommended intake for humans in a report that did not distinguish between omega-6 and omega-3 fatty acid needs.[16] Although, like linoleic acid, linolenic acid cannot be synthesized in mammals, the administration of the latter can only reverse some but not all the clinical manifestations of EFAD. Some of the clinical features of EFAD, which the administration of linolenic acid has failed to reverse, include reproductive failure and skin permeability.[9,10] An assessment of the overall efficacy of linolenic acid as an EFA shows, for instance, that it is only 10% as potent as linoleic acid in reversing the skin changes of EFAD.[8] However, the position of linolenic acid as an EFA appears to be strengthened by the report by Holman et al.[17] that shows the neurological symptoms developed by a 6-year-old girl maintained on total parenteral nutrition (TPN) after bowel resection disappeared when the TPN fat-emulsion was switched from one enriched with linoleic acid but poor in linolenic acid to one with high contents of the latter and low concentrations of the former. While the debate on the essentiality of linolenic acid in humans continues, the suggestion by Holman[18] that the concept of a balanced diet must include a consideration of balanced concentrations of several polyunsaturated, monounsaturated, and saturated fatty acids is a useful guidance. It has also been suggested[8,19-22] that an optimum ratio of linoleic acid to linolenic acid may be an important consideration in the dietary benefits of these fatty acids.

This article will review the effect of omega-6 and omega-3 fatty acids on pancreatic hormone release and how this may be involved in some of the known metabolic benefits of the fatty acids in general and particularly during TPN. Also, the metabolism of these fatty acids and the possible roles played by their metabolic products in signal transduction for insulin secretion will be discussed. Recent studies have shown that there may be preferential metabolic pathways for the various fatty acids based on their chain length and degree of unsaturation. For example, it is now known that the rate of activation and oxidation of fatty acids is greatly dependent on the degree of unsaturation, as an enhanced cellular uptake and oxidation correlates with the degree of unsaturation.[23-26] Generally, the metabolism of EFA follows two pathways: (1) beta oxidation in the mitochondria or peroxisomes,[27] (2) biosynthesis of membrane phospholipids, leukotrienes, and prostaglandins.[5] The factors that determine which of these pathways predominates at any given time include the degree of unsaturation, the presence of other fatty acids that compete for the same enzymes, and the type of tissue processing the fatty acids.[7,8,28] Essential fatty acids become components of phospholipids either by direct incorporation or by elongation and desaturation to form longer chain polyunsaturated fatty acids, which are then incorporated into phospholipids.[8,28-30] The metabolism of omega-6 and omega-3 fatty acids involving elongation and desaturation in humans and animals is shown in *Figure 1*, which outlines the metabolism of EFAs via both the degradative and biosynthesis pathways. In the biosynthetic pathways the same enzymes (desaturases and elongases) catalyze the metabolism of omega-6 and omega-3 fatty acids, whose dietary precursors are linoleic acid and linolenic acid, respectively. The metabolism of the omega-6 series generates arachidonic acid, which is either incorporated directly into membrane phospholipids or further metabolized in one of two pathways; namely the lipoxygenase pathway to yield leukotrienes or the cycloxygenase pathway to yield prostaglandins. The degradative pathway for linoleic acid processing involves its entry into the cell mitochondria or peroxisomes for beta-oxidation to acyl-CoA intermediates and ATP. It is known that because of its inherent

ease of oxidation, most of the dietary linolenic acid is used as fuel, although some is incorporated into phospholipids and cholesteryl esters, and very little is elongated and eventually converted to prostaglandins.[19] Thus, as shown in *Figure 1*, the biosynthetic pathway for the metabolism of the omega-3 series essentially yields the predominant constituent fatty acids of fish oils; namely eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), which are subsequently metabolised in the lipoxygenase and cycloxygenase pathways to generate families of leukotrienes and prostaglandins that are different from those generated by the omega-6 series. Most of the dietary linolenic acid will, however, be processed in the mitochondrial oxidative pathway shown in *Figure 1*. As already mentioned, some products of both the catabolic and anabolic pathways have been implicated in the signal transduction/secretion coupling for pancreatic beta cell insulin release, and this will be discussed further in a later section of this article.

Effect of fatty acids on islet hormone release

It has recently been pointed out that the exact role of fatty acids in insulin release remains an enigma.[31] This statement is an accurate reflection of the enormous controversy that exists on this subject when one examines the data from previous work. Thus, while some studies showed a stimulatory effect, others failed to show any effect on insulin secretion.[32] The main reasons for this controversy have been: (a) lack of differentiation between the various fatty acids and (b) nonuniformity in the methodology for studying the effect of fatty acids on insulin secretion. Recent work using physiologic techniques, such as the isolated perifused islets, have now provided some clues on the role of fatty acids on insulin release. In the new studies, fatty acid structural characteristics such as chain length and degree of unsaturation have been taken into consideration. Thus, it has been consistently shown in both humans and animals that polyunsaturated fatty acids stimulate insulin release in vivo and in vitro.[30,33–38] In addition, these polyunsaturated fatty acids appear to stimulate glucagon secretion at high concentrations that have potent stimulatory effects on insulin secretion in the presence of basal glucose,[39] probably as a counterregulatory safeguard against the risk of hypoglycemia. In other words, the profound stimulation of insulin release stimulated by high concentrations of polyunsaturated fatty acids may be countered by stimulation of glucagon secretion, which would be necessary to raise blood glucose levels by enhancing glycogenolysis. It has also been shown that long chain saturated fatty acids, depending on their chain length, may either have no effect or a depressive effect on insulin release because palmitate was without effect, while stearate caused a decrease in basal insulin output in perfused islets.[40] In this later study, it was observed that following withdrawal of palmitate from the perifusate, both basal and glucose-stimulated insulin release was enhanced and this may explain the palmitate-induced increment in insulin secretion observed during static incubations of islets with this fatty acid.[41] It has been suggested that palmitate might amplify the insulin secretory response of islets to glucose by stimulating "de novo" synthesis of phosphoinositides and the subsequent generation of inositol phosphates, which would contribute to accelerated calcium turnover and the concomitant release of insulin.[41] There is a consensus between previous studies that show that some medium chain fatty acids (eight to 12 carbon atoms), either free or esterified into medium chain triglycerides (MCT), enhance insulin release.[42,43] The stimulation of insulin secretion by medium chain fatty acids (MCFs) has been recently confirmed in a study[44] that shows a linear relationship between MCF chain length and stimulatory effect on insulin secretion, as illustrated in *Figure 2*. Thus, in experiments to examine the effects of 5 mM of each MCF, while adipic acid (C6:0) had no effect and octanoate (C8:0) had only a modest effect, capric acid (C10:0) and lauric acid (C12:0) had very potent stimulatory effects on insulin output by isolated perifused mouse islets *(Figure 2)*. A recent study has suggested that MCT may be a promising adjunct to conventional dietary and sulfonylurea treatment in non-insulin-dependent diabetes mellitus.[45] It is possible that the efficacy of MCT demonstrated in that study may be attributable to the stimulatory effect of the MCF on insulin release and the subsequent effect of insulin in enhancing glucose disposal.

Mechanisms of EFA-induced pancreatic hormone release

Currently available data suggest that multiple mechanisms exist by which EFAs may stimulate insulin release. As shown in *Figure 3*, among the possible pathways for EFA metabolism in the islet cells are: (a) direct incorporation into membrane phospholipids, (b) desaturation and elongation and subsequent entry into de novo synthesis of phospholipids, (c) oxidation and concomitant generation of metabolic energy. These processes generate metabolites such as arachidonic acid, diacylglycerol, inositol 1,4,5-triphosphate, long chain acyl-CoA, and ATP, which have now been implicated as mediators of nutrient-stimulated insulin secretion.[46–54] Specifically, it has been shown that the stimulatory effect of EFAs on insulin secretion is linked to their intramitochondrial beta-oxidation in the pancreatic beta cell.[35–38] In these reports, specific inhibitors of acyl-CoA transferase (the enzyme that catalyses the entry of fatty acids into the beta cell mitochondria) were used to inhibit the EFA-induced increase in insulin secretion. Thus, as shown in *Figure 4*, the addition of a mixture of linoleic acid and linolenic acid to a basal glucose perifusate augmented insulin release. When the EFA mixture was added in the presence of palmoxirate (fatty acid oxidation inhibitor), the fatty acid-stimulated insulin secretion was profoundly inhibited. The inhibition by palmoxirate of the EFA-induced effect on insulin release was immediately followed by a rebound "off-response" in basal insulin secretion on withdrawal of both the fatty acid mixture and the inhibitor *(Figure 5)*.

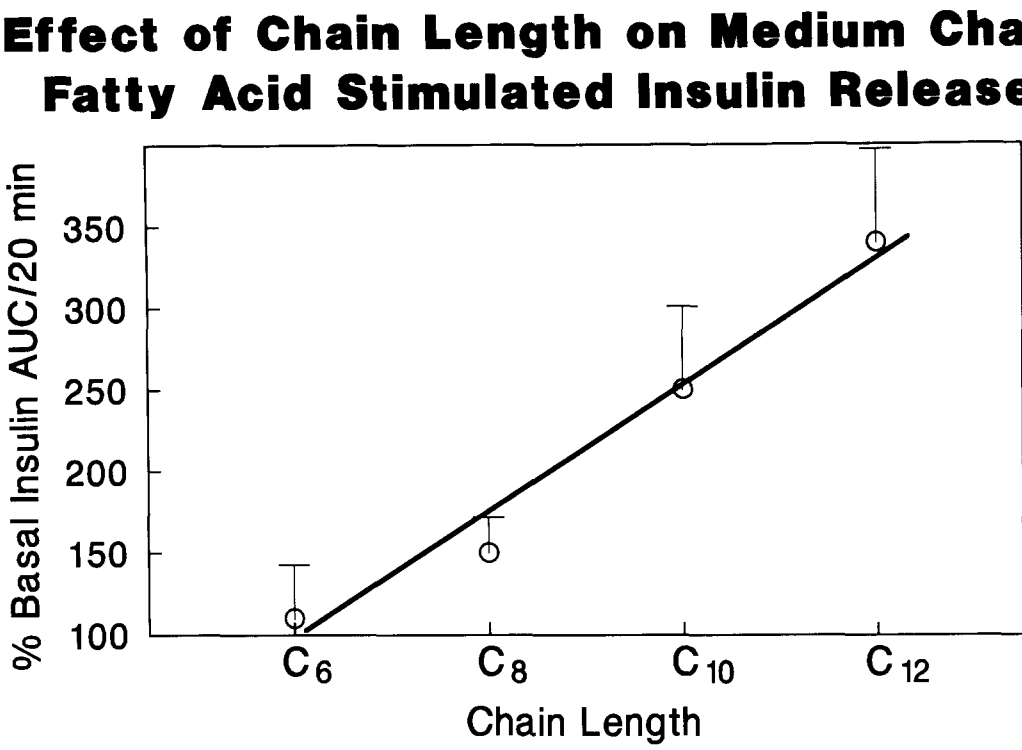

Figure 2 Effect of chain length on medium-chain fatty acid stimulation of insulin release. The effect of 5 mM of each fatty acid was evaluated as mean ± SEM percentage of basal insulin area under the curve/20 min.

Additional experiments are needed to elucidate the post-inhibitory "rebound" phenomenon, but it could be speculated from this observation that when fatty acid oxidation was inhibited, the EFA processing in the beta cells entered into the synthesis of phospholipids whose hydrolysis become activated on withdrawal of the fatty acids from the perifusate, thus generating signals for enhanced insulin release. It is of interest that we have always observed a rebound in basal insulin secretion in the perifusion period immediately following a long chain (both saturated and unsaturated) fatty acid perifusion (data not shown). If indeed the "rebound" phenomenon involves phospholipid hydrolysis, these observations would be consistent with the hypothesis that fatty acids can also stimulate insulin secretion via mediators generated by pathways other than oxidation, such as the phospholipase C-mediated phospholipid hydrolysis.[48,49,54–57]

The link between fatty acid oxidation and stimulation of insulin secretion that has been described provides additional support for the growing evidence that ATP generation in nutrient metabolism is one of the mechanisms by which glucose stimulates insulin release.[58,59] According to this ATP hypothesis, there exists a particular class of K^+ channels that is inhibited by increases in intracellular pancreatic beta cell ATP concentrations.[60] The ATP-induced inhibition of K^+ channels on the beta cell plasma membrane depolarizes the membrane and opens up the Ca^{++} channels. An influx of extracellular Ca^{++} into the cytosol ensues, thus raising the intracellular Ca^{++} and setting in motion the cascade of events culminating in insulin secretion.[59] The main drawback for this hypothesis stems from confusion generated by the early observation that K^+ channels are so exquisitely sensitive to intracellular ATP that they are 99% inhibited under resting ATP concentrations (approximately 0.2 μM) in the beta cell. To explain this apparent discrepancy, a simple mathematical model has been used to propose a spare-channel hypothesis that actually shows the extreme sensitivity of the K^+ channels to be appropriate, possibly mandatory, for their physiological function.[61] It also has been suggested that the ratio of ATP/ADP may play a role in the metabolite-regulated K^+ channel coupling to insulin secretion.[58] A recent review of this subject has adopted the position that the links between glucose metabolism and the closure of ATP-sensitive K^+ channels remain to be fully understood, but proposes that ATP is a key second messenger, whereas other glucose metabolites may contribute to stimulated-insulin secretion.[61] As mentioned earlier, EFAs have also been shown to stimulate glucagon secretion simultaneously with stimulatory effect on insulin release, albeit with differences in the kinetics of the secretory responses.[36,39] The mechanism by which these fatty acids stimulate glucagon secretion is not clear. It is presently not known whether these fatty acids have any effect on the neurotransmitter gamma-aminobutyric acid (GABA), which has recently been shown to be involved in the regulation of pancreatic alpha cell function.[62] One possible explanation for the effect of the fatty acids on glucagon secretion may involve changes in the pancreatic alpha cell ATP levels, as previously suggested.[63,64] Because it has been shown that prostaglandin E_2 simultaneously stimulates both insulin and

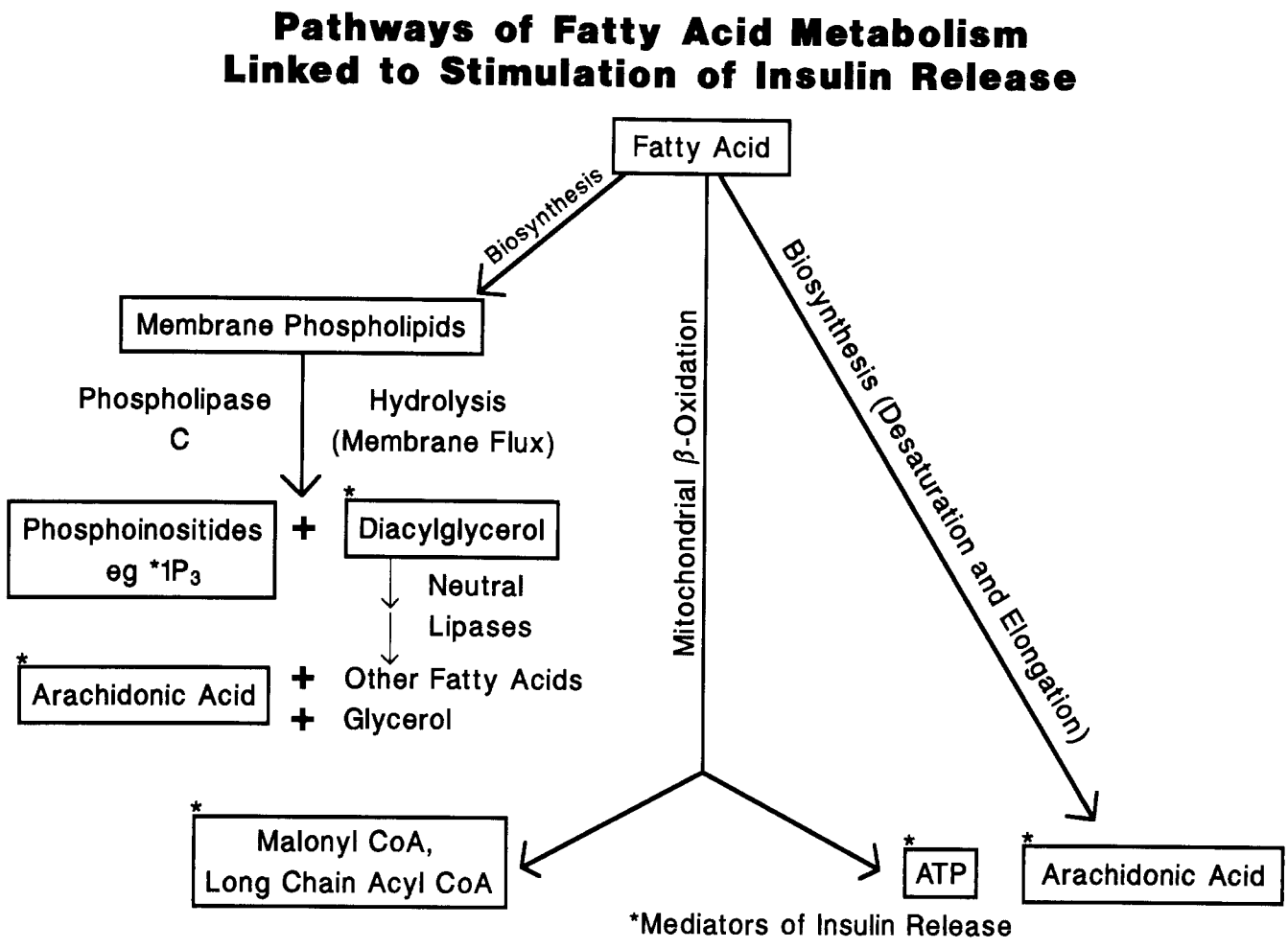

Figure 3 Outline of link between fatty acid metabolism and insulin release. This figure illustrates the relationship between fatty acid metabolism through different pathways and the generation of mediators of stimulated insulin secretion.

glucagon,[65] it seems plausible to suggest that the metabolism of EFAs in the pathway leading to prostanoid synthesis shown in *Figure 1* may also play a role in the EFA-stimulated release of these pancreatic hormones.

During phospholipid biosynthesis, inositol is rapidly and exclusively incorporated into the subclass of phospholipids called phosphoinositides.[66,67] Upon stimulation, these phosphoinositides are hydrolysed enzymatically by phospholipase C mediation, thereby generating a complex array of inositol phosphates along with diacylglycerol (DAG). Over 20 different inositol phosphates have been identified so far.[54] Of these, only inositol 1,4,5-triphosphate (IP_3) has shown promise as a second messenger for stimulated insulin secretion.[48,54,56] IP_3 is known to mobilize Ca^{++} from storage sites in the beta cell endoplasmic reticulum.[48,56] However, it is currently thought that IP_3 is a positive, though not independent, mediator of insulin release.[56] The other product of phosphoinositol hydrolysis, DAG, is known to activate protein kinase C (PKC), whose role in nutrient-stimulated insulin release is presently controversial.[48,54,68,69] Initial studies showed that the phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA), activates PKC and subsequently induces insulin secretion in perifused islets.[48,70,71] It was later shown that TPA can substitute for endogenous DAG in PKC activation.[54] One approach adopted by some investigators in the elucidation of the involvement of PKC in insulin secretion was to deplete the islet of this enzyme by prior incubation of islets with TPA.[72,73] These studies demonstrated that, while the subsequent response to TPA was lost, glucose-induced insulin secretion remained intact, leading to the conclusion that PKC may not be involved in glucose-induced insulin release. However, it has recently been argued[54] that these studies are flawed by a number of events, such as: (a) the existence of multiple forms of PKC, which may not be uniformly down-regulated by phorbol ester treatment, (b) substrate specificity of PKC may be altered by TPA pretreatment, (c) multiple mechanisms for the insulinotropic effect of TPA, and (d) use of static incubations of islets rather than perifused islets in insulin secretory studies. Additional work that would consider all these issues when evaluating the participation of PKC in insulin secretion is required, although Zawalich et al. have recently taken the position that PKC activation is intimately involved in glucose-stimulated insulin secretion.[54]

Arachidonic acid (AA) is both a biosynthetic product of linoleic acid metabolism as well as a byproduct of phos-

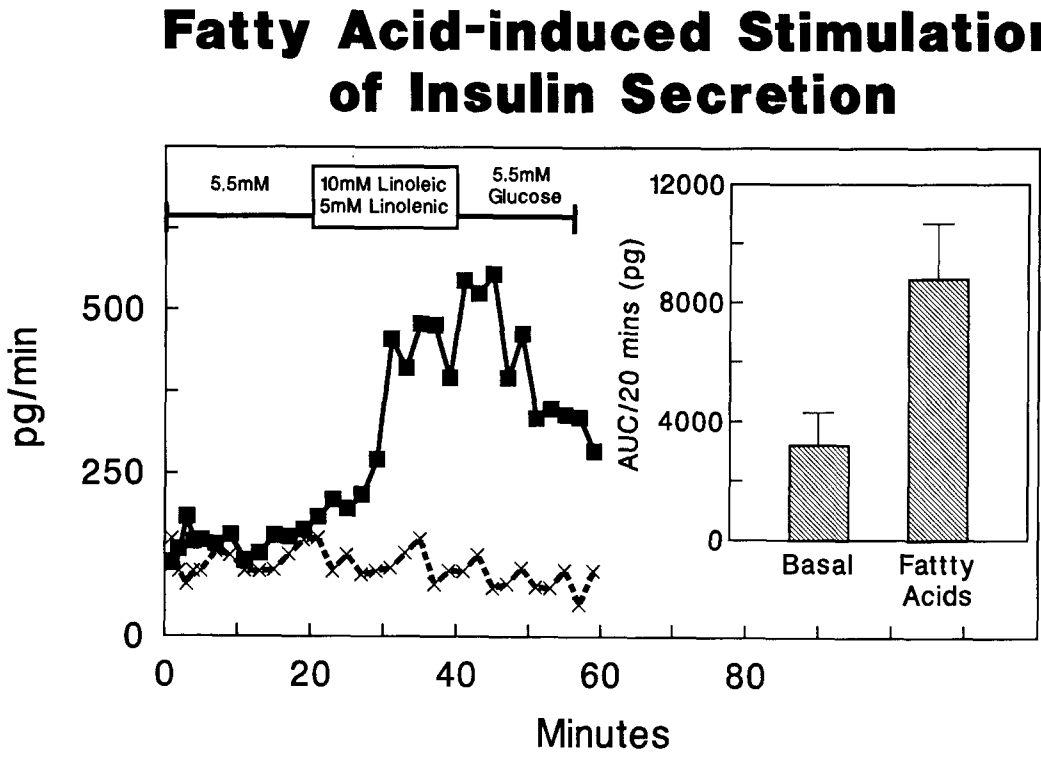

Figure 4 Polyunsaturated fatty acid stimulation of insulin secretion. The stimulatory effect of a mixture of linoleic acid and linolenic acid was demonstrable when the fatty acids were added to basal glucose perifusate. Reproduced with permission from Opara et al.[36]

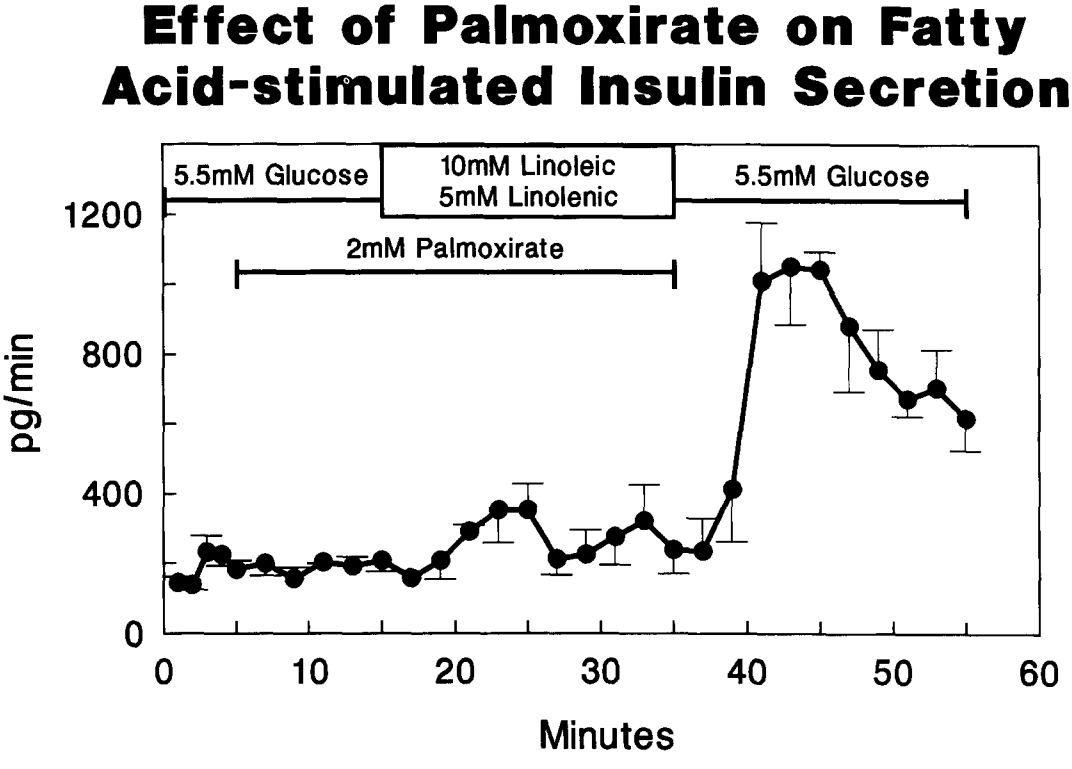

Figure 5 Inhibition of fatty acid-stimulated insulin secretion by palmoxirate. The inhibition of fatty acid beta oxidation with palmoxirate was associated with the loss of fatty acid-stimulated insulin release. Reproduced with permission from Opara et al.[36]

pholipid hydrolysis, and has been implicated as a mediator in stimulated insulin secretion.[46–48] The stimulatory effect of AA on insulin secretion is thought to be linked to the synthesis of a 12-lipoxygenase product, presumably the hydroxylated analogue (12-HETE) of 12-S-hydroperoxyeicosa-5,8,10,14-tetraenoic acid (12HPETE) from the AA precursor.[46,48,53] However, the mechanism of 12-HETE–mediated insulin release remains unclear. It also has been suggested that AA may promote insulin secretion by activating PKC.[74]

Of interest in the consideration of the mechanism of EFA-stimulated insulin release is the recent suggestion that malonyl-CoA and long chain acyl-CoA serve as metabolic coupling factors in signal transduction when islets are stimulated by high glucose or glucose combined with other fuels.[75] Because these CoA compounds are intermediates of fatty acid metabolism, this report is consistent with our observation of a stimulatory effect of EFA on insulin release.[36–38]

Although studies remain to be done to work out the intricate details of action of the various mediators involved in stimulated insulin release, it does appear that, as summarized in *Figure 6*, the unifying mechanism for almost all of them entails a rise in the beta cell cytosolic Ca^{++} prior to the exocytosis of insulin.[76]

Relationship between EFA-induced pancreatic hormone release and the efficacy of these nutrients in TPN

Traditionally, stressed patients in critical care, including postoperative patients, were infused with an all-glucose solution for caloric support. While this TPN regimen provided adequate metabolic energy, the patients developed a variety of problems with prolonged administration of this solution. Among these problems were EFAD, which was demonstrable within 5 days of starting fat-free TPN;[77,78] metabolic complications of glucose intolerance; and abnormally elevated hepatic enzymes.[79,80] The importance of the administration of fat emulsions became apparent when it was shown that in addition to supplying EFAs, these lipid emulsions could provide 30–50% of nonprotein energy as well as correct the glucose intolerance that ensued during all-glucose TPN.[80] It is pertinent to highlight the importance of the provision of adequate amounts of essential fatty acids in these lipid emulsions for TPN to allow for the rapid oxidation of these polyunsaturated fatty acids,[23–25] leading to the enhanced metabolic energy yield of lipid emulsions as well as ensure the prevention of the development of EFAD. It can also be speculated that the simultaneous stimulatory effects of high concentrations of EFA on insulin and glucagon release[39] may help regulate the plasma insulin to glucagon molar ratio in such a way as to prevent a disorder in glucose homeostasis during TPN.

An emerging area of investigation is the recently described PUFA-induced desensitization of pancreatic beta cell response to glucose through a process probably linked to fatty acid oxidation.[35,37,81] In isolated perifused mouse islets, the stimulatory effect of 27.7 mM glucose on insulin release by untreated islets was lost after these islets had been exposed to a linoleate perifusate in the absence of L-glutamine *(Figure 7a)*. In these experiments, linoleate caused a potent stimulatory effect on insulin secretion *(Figure 7a)*. When L-glutamine was added to the linoleate perifusate, glucose-stimulated insulin release was present before and after the fatty acid

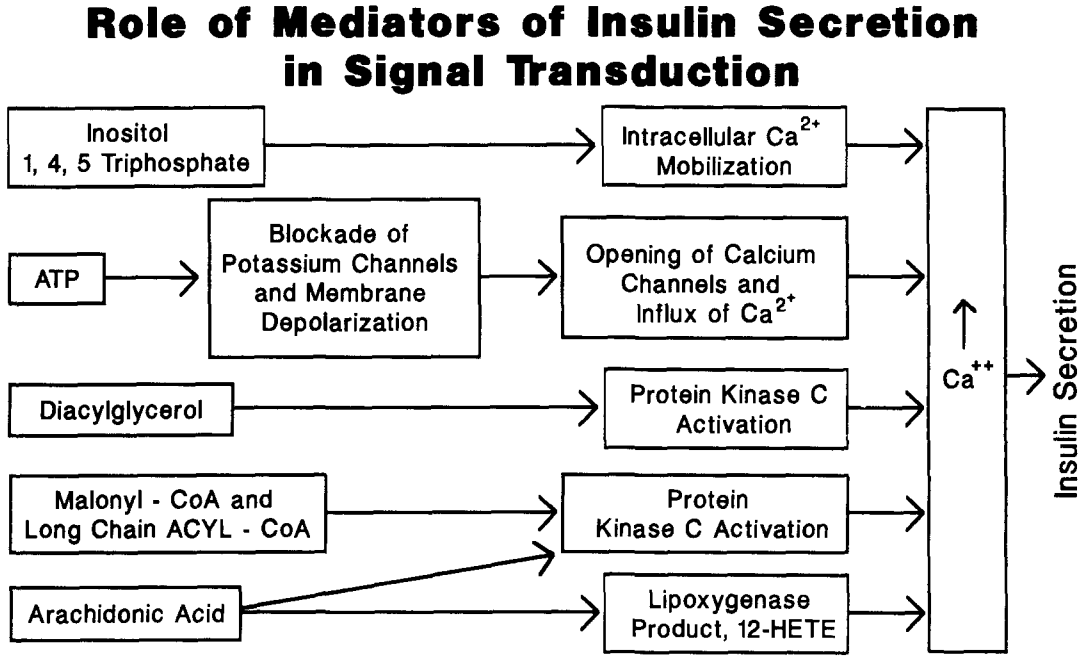

Figure 6 Role of mediators of insulin secretion in signal transduction. This sketch summarizes the mechanism by which the different mediators generated during fatty acid metabolism are thought to influence insulin secretion.

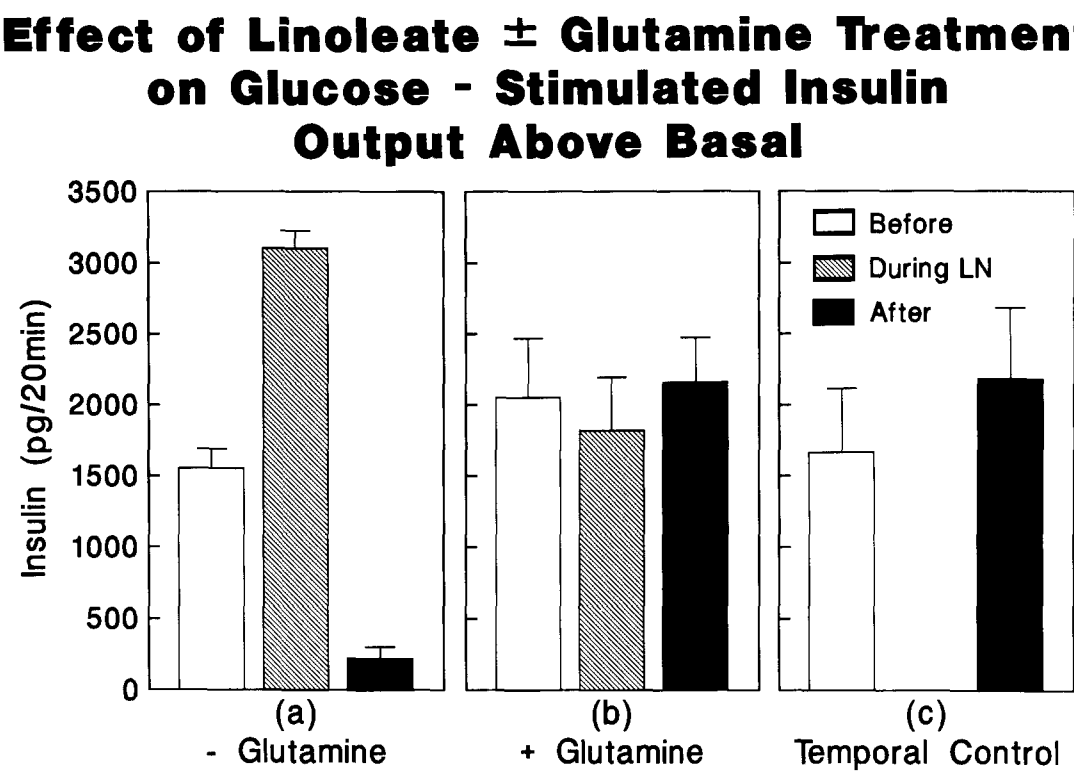

Figure 7 Effect of linoleate ± L-glutamine treatment on glucose-stimulated insulin release. Islet insulin response to 27.7 mM glucose before and after exposure to the fatty acid was examined. Reproduced with permission from Opara et al.[102]

exposure, and the stimulatory effect of linoleate on insulin output was attenuated *(Figure 7b)*. In temporal control experiments during which some islets were simultaneously perifused with basal glucose over the time-course of these perifusions, glucose-induced insulin secretion at the beginning and end of perifusion was preserved *(Figure 7c)*. The phenomenon of PUFA-induced desensitization of islets to glucose occurs slowly in vivo[35] but quite rapidly in vitro,[37,80] probably because in vivo there is an abundant supply of antioxidants such as vitamins C and E, glutamine, and glutathione to counteract the deleterious effect of oxidation stress on glucose-induced insulin release. The rapid occurrence of desensitization in vitro is consistent with the rapid inhibition of glycolysis by peroxides, which are oxidative products of PUFA oxidation.[82,83] It is known that PUFA are very rapidly oxidized in the presence of oxygen, with the formation of peroxides and toxic free radicals; hence, they are protected by antioxidants such as vitamin E. Indeed, it has been suggested that antioxidants like vitamin E should be provided during periods of increased intake of PUFA.[29] In support of this proposal, in recent experiments it has been shown that substitution of L-glutamine with the antioxidant, glutathione, in the linoleate perifusate of isolated islets essentially yields similar results, leading to the conclusion that the efficacy of L-glutamine in blockade of PUFA-induced desensitization of islets may be linked both to its inhibitory effect on fatty acid oxidation[84] and the generation of glutathione,[85] an important antioxidant comprising glutamate, cysteine, and glycine.

The protective effect of tissue antioxidants may be the reason why this phenomenon is yet to be clinically apparent, although the not uncommon practice of addition of exogenous insulin to TPN solutions[86] would contribute to the prevention of the deleterious effects of desensitization. However, in the TPN setting desensitization of the islets remains a potential risk, particularly in malnourished patients on prolonged EFA supplementation, whose tissue levels of antioxidants may be depleted. Taken together, the present observations support the scheme outlined in *Figure 8* as a possible mechanism for the fatty acid-induced desensitization of beta cell response to glucose. As already described, glucose metabolism via glycolysis, and the Krebs cycle and the concomitant generation of ATP is thought to be a major pathway for glucose-induced insulin release. The perifusion of islets with PUFA would, by the process of beta-oxidation of the fatty acids in the mitochondria, generate much ATP and hydrogen peroxide (H_2O_2), which can be produced in the reactions of oxidative phosphorylation and the associated electron transport chain,[87] as well as by lipid peroxidation.[88] One of these products of PUFA oxidation, ATP, inhibits the phosphofructokinase (PFK) and pyruvate kinase (PK) enzymes,[89] whereas the other, H_2O_2, inhibits the glyceraldehyde-phosphate dehydrogenase (GPDH) enzyme[82,83] of glycolysis, resulting in the blockade of

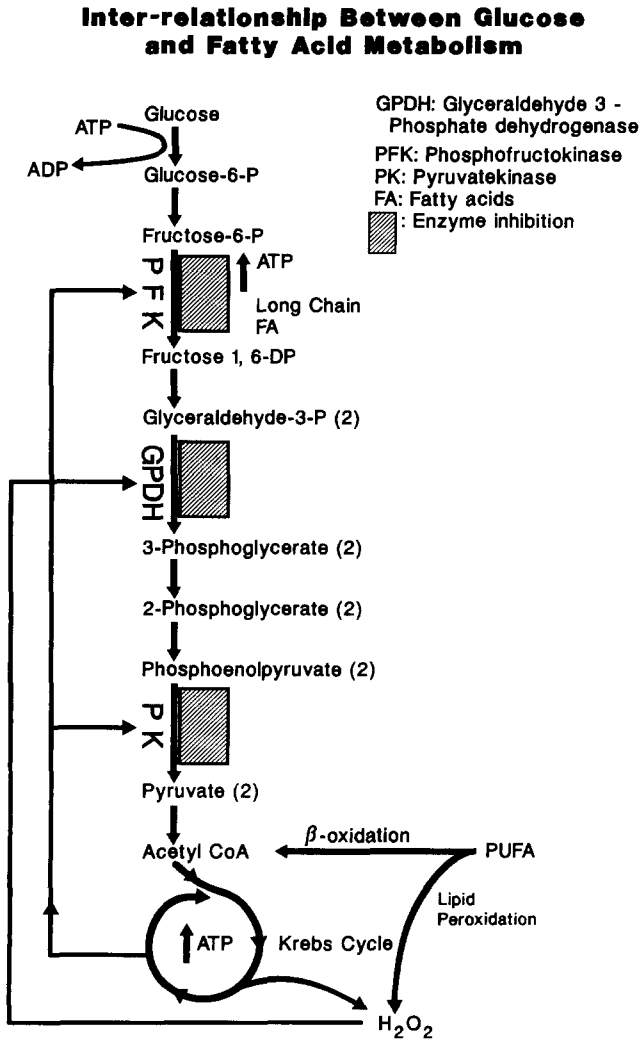

Figure 8 Interrelationship between glucose, fatty acid metabolism, and desensitization of islet response to glucose. Products of fatty acid oxidation can interfere with glucose metabolism and consequently affect glucose-stimulated insulin secretion. Reproduced and modified with permission from Opara et al.[37]

glucose metabolism and consequently eliminating glucose-induced insulin secretion. *Figure 8* illustrates the interrelationship between glucose and fatty acid metabolism, showing two pathways by which PUFA metabolism can generate ATP and H_2O_2 in one pathway, and H_2O_2 alone in the other. It is presumed that the blockade of beta oxidation will eliminate the production of ATP and a component of H_2O_2 produced in the electron transport chain[87] but will not affect the second component produced by lipid peroxidation.[88] However, because desensitization can be prevented by the availability of antioxidants as well as by inhibiting fatty acid beta-oxidation in isolated perifused islet preparations,[37,90] it is possible that the first pathway, which generates both ATP and H_2O_2, is primarily responsible for shutting down glucose metabolism and blocking glucose-stimulated insulin secretion. Two distinct pools of glutathione have been described, a labile cytosolic pool and a more stable mitochondrial pool, and it has been suggested that the depletion of the mitochondrial glutathione pool is a sensitive indicator of oxidative damage.[91] Because active mitochondrial oxidation of intermediate substrates of glucose metabolism is important in their stimulation of insulin release,[31] and fatty acid beta-oxidation occurs predominantly in the mitochondria,[92] it is conceivable that PUFA-induced desensitization involves the depletion of mitochondrial glutathione. The preservation of islet response to glucose after exposure to a PUFA perifusate containing glutathione[90] may therefore occur primarily by the replenishment of mitochondrial glutathione. These observations provide a metabolic rationale for the suggestion that an optimal balance between the content of unsaturated fatty acids and natural antioxidants in dietary oils is of major importance.[93] Indeed, it has also been suggested that antioxidant micronutrients should be measured when PUFA metabolism is studied, because further studies are required to elucidate the relationship between plasma fatty acids and antioxidant defense in disease states.[94] It also has been reported that monkeys were unable to compensate for increased peroxidative stress when fed diets with high contents of PUFA, but a four-fold supplement of vitamin E to the diets reduced the oxidation.[95]

It has been shown that the addition of insulin to TPN solutions increases the rate at which a malnourished state is corrected.[86] Another report has shown that polyunsaturated fats enhanced peripheral glucose utilization in rats,[96] an observation that may be ascribable to the enhancement of insulin secretion and subsequent stimulation of peripheral glucose utilization by insulin-sensitive tissues. It is also of interest that the supply of EFA has been shown to inhibit the hepatic synthesis of fatty acids.[97] EFAs can also act to prevent the development of fatty liver by inhibiting acetyl CoA carboxylase and glucose-6-phosphate dehydrogenase, causing the synthesis of fatty acids from glucose to be blocked.[98,99] Hepatic lipogenesis also is regulated by various hormones, particularly insulin, and the effect of insulin on hepatic fatty acid synthesis is secondary to its priming of glucose utilization.[100] It has been suggested that EFAD may be primarily responsible for the development of fatty liver during hyperalimentation.[100] A stimulation of glucagon secretion induced by high concentrations of EFA has been observed.[39] It is tempting to speculate that this increased glucagon secretion also may be of an additional benefit in preventing the development of hepatic steatosis in patients receiving TPN, because it has recently been proposed that an elevation of portal vein glucagon levels would enhance lipolysis and thus aid hepatic export.[101]

Conclusion

It is certain that EFAs have a direct potent stimulatory effect on pancreatic hormone release in acute experiments. Given the pivotal role of insulin in metabolic processes, it can be proposed that some of the benefits of the provision of EFA to critically ill patients receiving TPN derives from the stimulation of insulin secretion

by these fatty acids. The release of insulin induced by EFA may become particularly beneficial in postoperative patients receiving TPN because the released insulin, which promotes protein synthesis, would enhance tissue growth and repair. However, because there appears to be a potential risk for impairment of endocrine pancreatic function during prolonged administration of lipid emulsions to stressed patients, owing to metabolic oxidative and perioxidative stress causing the generation of deleterious levels of hydroperoxides, the provision of micronutrient antioxidants such as vitamin E, as well as nutrients that inhibit fatty acid oxidation and/or enhance glutathione synthesis such as glutamine, should be seriously considered, as recently proposed.[102] Finally, it can therefore be concluded that the provision of EFAs during hyperalimentation is desirable, both in regard to providing nutritional support and their potential role in control of metabolic events.

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