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Dietary fats, fatty acids and insulin resistance: short review of a multifaceted connection

Marianne Haag, Nola G. Dippenaar

Department of Physiology, University of Pretoria, Pretoria, South Africa

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Summary

Insulin resistance is a growing worldwide phenomenon, which progressively develops over years, and finally, if unchecked, predisposes to cardiovascular disease and diabetes mellitus type 2. Insulin resistance is a generalized metabolic disorder characterized by inefficient insulin function in skeletal muscle, liver and adipocytes. There is growing evidence that an increased free fatty acid level, and more importantly, the relative amounts of saturated and unsaturated fatty acids, plays an important role in the development of insulin resistance. In turn, this is a reflection of the composition of dietary fat. Ultimately both the dietary intake and plasma levels determine the fatty acid composition of cell membranes. Higher levels of membrane saturated fatty acids seem to greatly impair the action of insulin, whereas the presence of polyunsaturated fatty acids, especially of the omega-3 and -6 families, and in particular their relative ratio, in contrast, improves insulin sensitivity. *In vitro* studies, however, have not always corroborated the clinical evidence. Possible roles played by the various saturated and unsaturated fatty acids in the insulin-signaling pathway are discussed in light of recent evidence. Fatty acids have also been shown to alter gene expression in cells, in particular the peroxisome proliferator-activated receptor-γ2 gene, adding to this multifaceted connection.

As man has moved over the centuries from a hunter-gatherer diet to greater intakes of saturated and trans-fatty acids, insulin resistance has appeared with its related pathology. Greater understanding of the role played by dietary fat and plasma fatty acids in pathogenesis of insulin resistance, will allow for more timely prevention and improved treatment in the future.

key words: **omega-3 fatty acids • omega-6 fatty acids • polyunsaturated fatty acids • insulin resistance • glucose uptake • obesity**

Abbreviations: **DHA** – docosahexaenoic acid; **EPA** – eicosapentaenoic acid; **AA** – arachidonic acid; **SA** – stearic acid; **OA** – oleic acid; **CLA** – conjugated linoleic acid; **FFA** – free fatty acids; **PUFAs** – polyunsaturated fatty acids; **MUFAS** – mono-unsaturated fatty acids; **IRS** – insulin receptor substrate; **P1-3-K** – phosphatidylinositol-3-kinase; **PKB** – protein kinase B; **PKC** – protein kinase C; **GLUT4** – glucose transporter-4; **ICML** – intramyocellular lipid; **ISGU** – insulin-stimulated glucose uptake; **MRS** – magnetic resonance spectroscopy; **HECT** – euglycaemic clamp technique; **PPAR** – peroxisome proliferator-activated receptor; **UCP** – uncoupling protein; ω – omega

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Author's address: Prof M Haag, Department of Physiology, University of Pretoria, PO Box 2034, Pretoria 0001, South Africa, e-mail: marianne.haag@up.ac.za

BACKGROUND

The condition of insulin resistance is tightly coupled with obesity and cardiovascular pathology, these conditions are collectively called 'the metabolic syndrome' or 'syndrome X'. Incidence of the disease is increasing to epidemic proportions, especially in previously rural societies that are undergoing urbanisation, and throughout the western world. The ability of body tissue to react to insulin becomes progressively more compromised as it moves, maybe for ten to twenty years, through the stages of insulin resistance. Triglyceride deposits in muscle tissue increase while increased levels of triglycerides and free fatty acids are hallmarks of the plasma composition [1]. During this stage, insulin secretion also becomes higher in an effort to correct the condition, until the beta cells of the pancreas are depleted and cease production, resulting in full-blown type 2 diabetes mellitus [2].

Insulin resistance is usually defined on a metabolic level as inefficient insulin function in skeletal muscle, liver and adipocytes. This hampers the normal role of insulin whereby it causes increased muscle cellular glucose uptake, glycogen synthesis, and cessation of hepatic glucose production [3]. In the adipocyte, especially in the visceral and omental region, the process of triglyceride synthesis is negatively affected, and lipolysis remains unchecked, resulting in even higher levels of circulating free fatty acids [4]. To achieve these metabolic effects, the activity of many different role-players in the insulin-signalling pathway could be compromised: amongst others, phosphatidylinositol-3-K (PI-3-K), protein kinase B (PKB), protein kinase C (PKC) and also glucose transporter4 (GLUT4) activation could be affected. In addition, gene regulation of any of these transporters or enzymes may also be impacted on during insulin resistance.

This review focuses on the ever-increasing evidence that dietary fat and the resulting plasma and plasma membrane fatty acid profiles are instrumental in the development of metabolic syndrome: the higher the saturated fatty acid content of the three abovementioned parameters, the more insulin action is impaired. Interestingly, in contrast, the higher the content of polyunsaturated fatty acids of a chain-length of 20–22 carbons, more especially belonging to the omega-3 fatty acid family, the more insulin action is improved [5–7]. The action of different fatty acids on the insulin signalling process will be summarised in an attempt to obtain more clarity on this multifaceted phenomenon.

EVIDENCE FROM DIETARY STUDIES

High fat feeding has been presumed to be a cause of obesity and insulin resistance for at least twenty years [8]. However, the concept that "oils ain't oils" [9] slowly started emerging in the latter half of the eighties and it is now well established that the fatty acid profile of a dietary fat has far-reaching differential regulatory consequences in the human body. As seen clearly from the fatty acid atomic models presented in Figure 1, progressive desaturation of the fatty acid molecule leads to increased "kinkiness". Striking differences in the molecular configuration of oleic acid (MUFA), linoleic acid (omega-6 PUFA) and α-linolenic acid (omega-3 PUFA) make for different properties when built into a cell membrane, as shown in Figure 2. High saturated fat content of the membrane makes for rigid, unresponsive membranes, whereas increased desaturation makes for improved membrane fluidity and responsiveness [10].

Membrane lipid profiles are determined by dietary fat intake

Diets containing tallow (predominantly saturated fat), olive oil (mainly mono-unsaturated), sunflower oil (largely omega-6) and fish oil (omega-3-rich) are commonly fed in animal studies investigating the effect of dietary fat on insulin resistance and obesity. Cell membrane lipid composition is regulated by the fatty acid composition of dietary fat, as explained lucidly in a recent review by Hulbert and co-authors [11]: the membrane lipid profile is especially sensitive to fatty acids of the omega-3 and omega-6 families of polyunsaturated fatty acids, actually preferring to build in more omega-3's than omega-6's. This is more true in the case of cerebral synaptosomes and myelin [12] (brain phospholipids contain about 40% omega-3's) than in liver [13] and cardiac membranes [14]. The membrane saturated and mono-unsaturated fatty acid content, on the other hand, is not as dependent on the dietary fatty acid profile [12–14]. Similar responses to intake of various dietary fatty acids was reported in skeletal muscle [15,16] and adipose tissue[17]. Quantitatively the latter two tissues are the most insulin-responsive and the most instrumental in maintenance of normal plasma glucose levels. It is important to note that in obese individuals there is an increase by as much as 30–50% of total body glucose uptake in fat tissue [18]). Muscle and fat membrane PUFA content and omega-3/omega-6 ratio thus appears to be of prime importance in the aetiology of insulin resistance.

Dietary fats and insulin sensitivity

In animal studies an impressive body of evidence has established the connection between dietary lipids, membrane lipid profiles and insulin resistance [5,6,9,19–21]. A pioneering study from the laboratory of Storlien and coworkers in 1987 [9] showed that only the replacement of safflower oil (omega(n)-6) with fish oil (n-3) in rats being fed a high percentage sucrose and fat diet, was able to attenuate the development of insulin resistance. The hyperinsulinaemic, euglycaemic clamp technique, (HECT), is generally used in studies on insulin sensitivity. Two venous catheters are inserted into antecubital veins (one for the infusion of glucose and insulin, the other for blood sampling) and an insulin infusion, resulting in hyperinsulinaemia, is given. Arterialised blood glucose is measured every five min and then a dextrose infusion is started. The clamp is adjusted to keep the blood glucose levels euglycemic (5 mmole/L). The rate of whole body glucose uptake is calculated from the mean glucose infusion rate from 80–120 min, corrected for glucose space and normalised per kilogram of fat-free mass [22]. Subsequent research utilising the HECT technique together with the injection of radioactively labelled deoxyglucose to determine whole body insulin action, supported this theory: high saturated fat diets led to insulin resistance, whereas diets high in n-3, with a low n-6/ n-3 ratio, kept insulin action at normal levels [5].

In human subjects, reports in the early 90's from Feskens and coworkers showed that glucose intolerance could be improved by the same strategy [23,24] as described above.

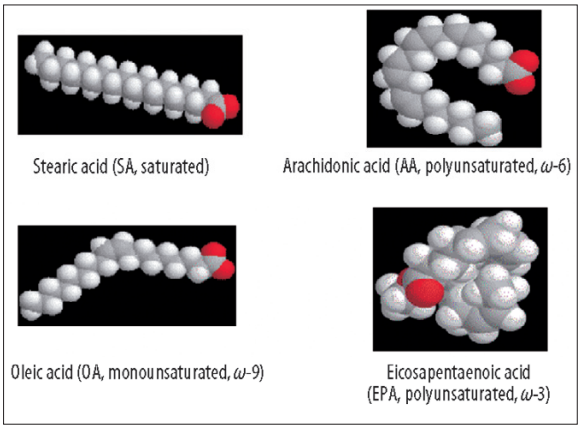

Figure 1. Atomic models of the saturated 18 carbon (C) stearic acid (SA), mono-unsaturated 18 C oleic acid (OA), polyunsaturated 20C omega-6 arachidonic acid (AA) and polyunsaturated 20C omega-3 eicosapentaenoic acid (EPA) [108].

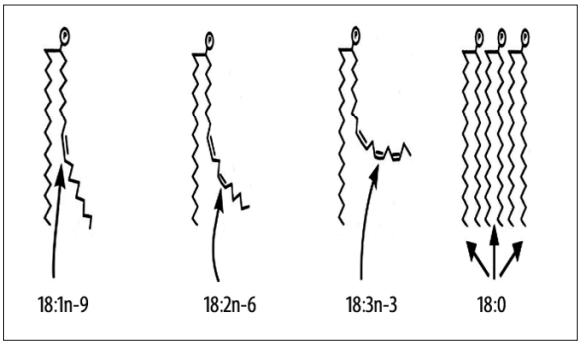

Figure 2. The degree of desaturation in fatty acids present in cell membrane phospholipids determines membrane fluidity. Saturated fatty acids, for example stearic acid (18:0, eighteen carbons, no double bonds) cause relatively solid domains in the membrane, oleic acid (18:1n-6), linoleic acid (18:2n-6), alpha-linoleic acid (18;3n-3) occupy increasingly more space and result in higher membrane fluidity. Adapted with permission from [10]: ©Medpharm Publications (Pty) Ltd.

Subsequently, a clear relationship between the amount of long chain, highly unsaturated fatty acids (C20–C22) in membrane phospholipids of vastus lateralis muscle and whole body insulin sensitivity (measured with HECT) could be demonstrated [19], as shown in Figure 3. This relationship was corroborated by studies on 70-year-old men in Sweden [25], in primarily Caucasian Australians and in indigenous American Pima Indians [26]. The obesity and Type 2 diabetes–prone Pima population proved to have 40% lower n-3 levels in their muscle membrane lipids than Australians. A further alarming wake-up call is that fasting insulin levels of pregnant women, indicating the level of maternal insulin resistance, can programme the degree of PUFA incorporation into their children's muscle membranes: the DHA content of baby boys' muscle membranes is inversely correlated with their mothers' fasting insulin levels. [27].

Very interestingly, regular physical exercise lowers levels of unsaturated (predominantly AA and DHA) fatty acids in skeletal muscle membranes, probably because these fatty acids are preferentially used for the oxidative needs of

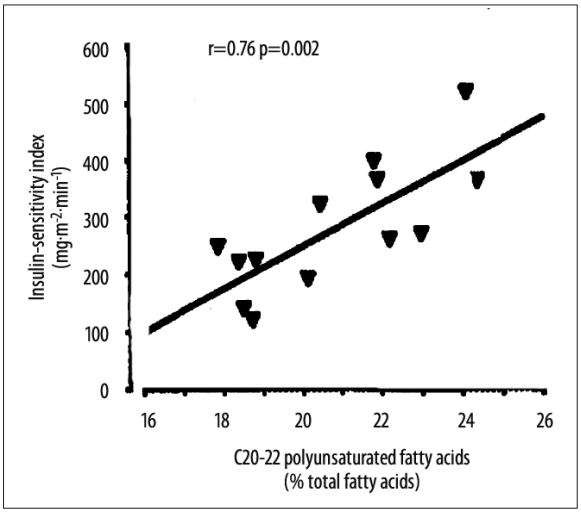

Figure 3. Relationship between the percentage of long-chain polyunsaturated fatty acids in the phospholipids of skeletal muscle (vastus lateralis) and whole-body insulin sensitivity determined by the hypeinsulinaemic, euglycaemic clamp technique. Reproduced with permission from [19]. ©1993 Massachusetts Medical Society.

muscle tissue. This progressively 'saturates' muscle membrane composition and would have a negative prognosis for insulin sensitivity [28]. However, this is at variance with the beneficial effects of exercise on muscle insulin sensitivity reported by Pereira et al. [29].

Increased intramyocellular lipid (ICML) stores are also inversely related to insulin action, both in animals [5] and humans [30]. Recent studies [31] have utilised the technique of ^{1}H magnetic resonance spectroscopy (MRS) to distinguish between extra- and intramyocellular fat deposits, and the same tight relationship between ICML stores and insulin resistance, measured with HECT method, was found. These results are shown in Figure 4. It is interesting that one of the more obese individuals (#1, BMI 32.8 kg/m^2), was one of the most insulin-sensitive, but had a low ICML value. Conversely, Subject #2, with a BMI of only 18.9 kg/m^2, proved to be highly insulin-resistant but had an larger ICML pool [1].

It has been suggested that it is not the triglyceride stores themselves in muscle that interferes with the action of insulin, but more likely fatty acid-derived entities, like long chain acyl-CoA's, that impacts negatively on insulin-mediated glucose uptake, by disrupting the insulin-signaling cascade [1]. The long chain acyl-CoA levels in a muscle cell are amongst others controlled by the malonyl CoA/carnitine palmitoyltransferase-1 partnership. In muscle, acetyl-CoA carboxylase-2 appears to associate closely with carnitine palmitoyltransferase-1 on the outer mitochondrial membrane [32]. As muscle cells have very low levels of fatty acid synthase, malonyl CoA is thought to act as a "fuel sensor", and thus a regulator of fatty acid oxidation [1]. Decreased capacity to oxidize fatty acids in muscle cells would result in an enlarged long chain acyl-CoA and triglyceride pool, and thus diminished insulin-mediated glucose uptake. Human and animal studies support the concept that a lower than normal capacity to oxidize fatty acids might be a predictor and/or contributor to the development of IR [1].

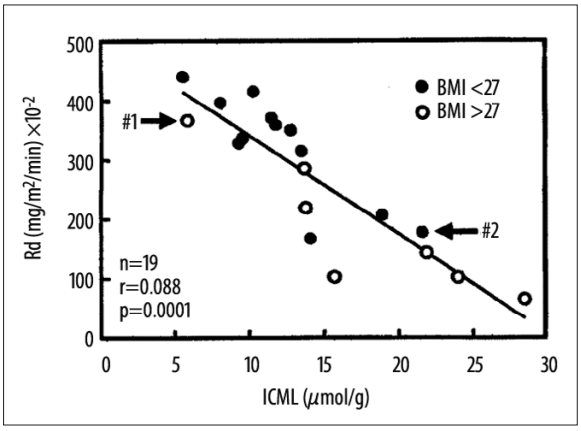

Figure 4. Correlation between measurements of ICML by ^{1}H MRS and the rate of insulin-stimulated glucose disposal (Rd) in normal glucose tolerance individuals who underwent a hyperinsulinemic-euglycemic clamp. Reproduced with permission from [1]. ©American Diabetes Association.

Lipid infusions and insulin sensitivity

In another avenue of clinical experimentation, plasma free fatty acids were artificially increased in normal individuals with lipid/heparin infusions. This strategy has also given rise to insulin resistance [33,34]. There is a lag period of about 5 hrs following commencement of infusion before the effect can be measured with HECT. By that time, ICML (measured by ^{1}H MRS) had risen by 61% in the tibialis anterior and by 22% in soleus muscles, and whole–body glucose uptake was reduced by 40–50% [35]. Using the same technique, Homko and coworkers [36] have shown that, even at insulin and free fatty acid levels in the average postprandial range, both healthy men and women are prone to periods of muscle and hepatic insulin resistance following meals.

In conclusion, free fatty acids are not only detrimental but also essential for insulin secretion, but chronic exposure of the β-cell to high free fatty acid levels can become toxic [1,37]. This could, at least partly, explain the progression of metabolic syndrome from the stage of insulin resistance with characteristically high insulin levels to pancreatic β-cell dysfunction and ultimately depletion, resulting in frank diabetes mellitus type 2.

Fatty acids and glucose uptake

In an excellent study Fickova et al. [17] has shown that PUFAs modulate insulin sensitive glucose uptake (ISGU) in isolated adipocytes: increased ISGU was more apparent in rats fed omega-6 rich diets (sunflower oil) than in rats fed omega-3 (fish oil) for one week. Unfortunately, data on saturated fat effects were not included in this paper. Ryan and coworkers [38] also presented evidence that feeding human subjects oleic acid for 2 months could improve ISGU in their isolated adipocytes. In contrast, a data from an older study by the group of Nagy and coworkers [39] had shown that feeding rats DHA (omega-3) and safflower oil (omega-6 rich) diets for three weeks had impaired their adipocyte ISGU. Reasons for these changes in ISGU may be found in the mechanisms of glucose transport: Insulin-stimulated glucose uptake (ISGU) is achieved with the glucose transporter GLUT4. During basal conditions GLUT4 is stored in vesicles that are transported to the cell membrane when stimulated by insulin. Defects in the GLUT-4 trafficking process after high fat (55% of total calories, of which 30% were saturated) feeding have been reported in murine muscle [40]. This trend was also seen in rat adipocytes [41]. Even during overexpression of GLUT4 in transgenic mice, severe insulin resistance has been found [42] after feeding the same high fat diet mentioned above. This would suggest that defective GLUT4 transport and not synthesis is at the root of the problem.

In vitro work, that is, exposing 3T3-L1 fat cell cultures or freshly isolated adipocytes to different fatty acids, has added a conflicting plethora of results to our knowledge. Already in 1981, Grunfeld and coworkers showed that the saturated palmitic acid could decrease ISGU [43] in 3T3-L1 cultures after a short exposure (<30 min). In contrast, when fresh rat adipocytes were directly exposed to fatty acids, Joost and Steinfelder [44] reported that palmitic, lauric, caprylic and caproic acids could all increase ISGU. Later studies reported that ISGU had not been affected by short-term exposure to fatty acids [45,46]. Moving to longer exposure times, Nugent and coworkers from the laboratory of O'Rahilly [47] have shown that 4–8 hrs of exposure to AA resulted in increased ISGU and GLUT4 content of plasma membranes. The use of mixed conjugated linoleic acid (CLA) isomers in glucose uptake studies in this type of experiment has not led to congruent data [48]. A recent paper from the same group, however, concluded that specifically the *trans*-10, *cis*-12 CLA isomer could decrease ISGU [49].

An interesting aspect that emerges from these studies is the fact that short-term fatty acid exposure can increase basal, thus insulin-independent, glucose uptake (BSU). Palmitic, lauric, caprylic and caproic acids [44], palmitic acid, linoleic and oleic acids [45,50] and according to Hunnicut [46] and coworkers only palmitic acid, but not linoleic, elaidic and oleic acids could all increase BSU. More recent studies have shown an important role specifically for arachidonic acid in stimulation of BSU after 4–8 hours of exposure [47,51,52]. What this means in terms of glucose homeostasis remains to be determined.

Dietary fats and energy balance

The intake of dietary fat, irrespective of its composition, has popularly been associated with weight gain. However, several studies in animals have shown that the intake of unsaturated fats (both of the omega-6 and omega-3 variety) does not lead to the same weight gain as an isocaloric saturated fat diet would have done. [16,53–56]. The same results have been found in humans, [57–59] in which the intake of saturated fat has also been linked to an increased central fat deposit as reflected in waistline measurements [60].

A number of mechanisms may explain the influence of individual fatty acids on fat accumulation. Leyton and coworkers had already shown in 1987 [61] that unsaturated fatty acids are more easily oxidised than their saturated counterparts in a study where labelled CO_2 was measured after ingestion of equal amounts of differently labelled saturated and unsaturated fatty acids. In addition, lipolytic stimuli liberated unsaturated fatty acids from triglyceride depots more easily than saturated fatty acids [62]. In addition, increasing the

degree of desaturation for a given fatty acid chain length increased the ease of liberation by lipolysis [63].

Furthermore, the intake of saturated fats can also decrease the basal metabolic rate [64,65]. The membrane sodium pump (Na^+, K^+-ATPase) accounts for a large fraction of the energy consumed under basal conditions [11] and, very interestingly, the molecular activity of Na^+, K^+-ATPase can also be positively correlated with membrane polyunsaturates as reflected in DHA (omega-3) content [66]. Citing another interesting enzyme system impacting on energy metabolism, Kopecký and coworkers have shown that impairment of the mitochondrial uncoupling protein (UCP) system can lead to obesity and thus insulin resistance. Synthesis of UCP's is regulated by the peroxisome proliferator-activated receptor-γ (PPAR) transcription factor family, which, in turn, can be regulated by fatty acids [67].

Another scenario that has to be considered in the development of obesity is the regulation of food intake. The classic feeding and satiety centres respectively located in the ventromedial and dorsolateral hypothalamic areas can also be influenced by the dietary fatty acid profile: intake of saturated fats by mice increased neuronal activity in the feeding centre, whereas PUFA feeding increased satiety centre activity [68]. Furthermore, leptin is an adipocyte hormone that acts on the arcuate nucleus to block secretion of the obesogenic neuropeptide Y, thus increasing satiety. Cha and Jones have shown in 1998 [69] that increasing diet PUFA levels could lead to increased plasma leptin levels when compared with a diet rich in saturated fats, thus further supporting the line of evidence in favour of the anti-adiposity role of PUFAs.

FATTY ACID ACTION: POSSIBLE MECHANISMS

Insulin resistance can be due to dysfunction of one or more of the intermediates of the insulin signaling cascade shown in Figure 5. Understanding the mechanisms involved in insulin resistance is imperative for the development of preventative or pharmaceutical strategies.

Eicosanoid production

Certain polyunsaturated fatty acids, but not saturated fatty acids, can be converted to eicosanoids by cyclooxygenase: for example, AA (omega-6) can be changed to the highly inflammatory prostaglandins of the -2 series, whereas EPA (omega-3) can be changed to anti-inflammatory prostaglandins of the -3 series. DHA (omega-3) cannot be converted to a prostaglandin, but retroconversion to EPA, and thence formation of series -3 prostaglandins, is possible [70]. Further downstream, omega-3 fatty acids are also precursors of the anti-inflammatory resolvins and docosatrienes as described by Serhan et al [71]. Different authors have implicated eicosanoids in regulation of GLUT4 trafficking and thus insulin-stimulated glucose transport [72,73]. In contrast, Nugent et al. [47] have reported a cyclooxygenase- independent stimulatory effect of AA on glucose uptake.

Protein Kinase C modulation

Fatty acids can modulate the action of protein kinase C (PKC) [74,75] Involvement of this enzyme in the signalling pathway has been well established, and changes in its activity possibly contribute to IR [76-78]. A widely accepted mechanism of fatty acid action has been proposed by Shulman in 2000 [79]. Activation of muscle PKC by fatty acid infusions can lead to increased serine/threonine phosphorylation of the insulin receptor substrate (IRS, as seen in Figure 1). This conformational change leads to decreased tyrosine phosphorylation of the IRS, thus impairing the whole downstream insulin signaling pathway and causing insulin resistance. The action of fatty acids on PKC seems to be isoform- and also organ-specific: muscle (beta II and delta [80], epsilon [81], theta [82]), and in adipocytes zeta [83,84] isoforms of PKC have been implicated in this mechanism. Interestingly, PKC is also implicated in the action of fatty acids on basal glucose transport via activation, and also synthesis, of insulin independent GLUT1 [51,52] thus suggesting PKC effects directly on glucose transporter activity.

Effects on phosphatidylinositol-3 kinase and protein kinase B

Activation of phosphatidylinositol-3 kinase (PI-3-K) is one of the important steps in insulin signaling downstream of IRS; indeed, the selective PI-3-K inhibitor wortmannin is able to abolish the translocation of GLUT4 to the cell membrane in response to the insulin signal [85,86]. Fatty acids have a profound effect on its activity; indeed, fatty acid infusions have caused total inhibition of the PI-3-K response to insulin [87]. Whether fatty acids act on PI-3-K directly, or whether their effect is exerted via PKC with subsequent inhibition of the insulin signal downstream of IRS as discussed above [80], is still unclear. Focussing on another intermediate in the insulin signalling pathway, protein kinase B activity may be reduced, and thus impair glycogen synthesis [88,89] or may not be affected [90] by saturated fats.

Fatty acids and gene expression

The modulation of gene expression by fatty acids is an area of great current interest and is widely believed to be the most important long term fatty acid action mechanism. In 1994, studies on 3T3-L1 cells had shown that glucose uptake via GLUT4 could be downregulated already after 4-8 hours of exposure to AA [91]. Indeed, after 48 hrs of AA exposure, GLUT4 mRNA was decreased by 90%. [92]. This study also provided evidence that the non-metabolizable analog of AA, eicosatetraenoic acid, could activate the PPAR γ transcription factor, a well-known modulator of adipocyte gene expression, under the same conditions. Mutation-related impairment of PPAR γ function can result in insulin resistance and diabetes mellitus type 2 [93,94], whereas stimulation of the PPAR-α form inhibits lipid accumulation and improves insulin signalling [95]. Recent studies have supported the concept that polyunsaturated fatty acids [9,47,93], can act as ligands of PPAR γ or modulate its expression, thus increasing GLUT4 transcription [96,97] and synthesis, and thus also improving insulin resistance. An increased perinatal dietary n-6/n-3 fatty acid ratio can programme mean body weight and fasting insulin levels to increase during later life in male rats specifically, acting on the mechanism of gene expression, as recently shown by Korotkova et al. [98] and reviewed by Das [99]. In a ground-breaking study, microarray technology data from the laboratory of Berger et al. [100] has shown that dietary supplementation of either ara-

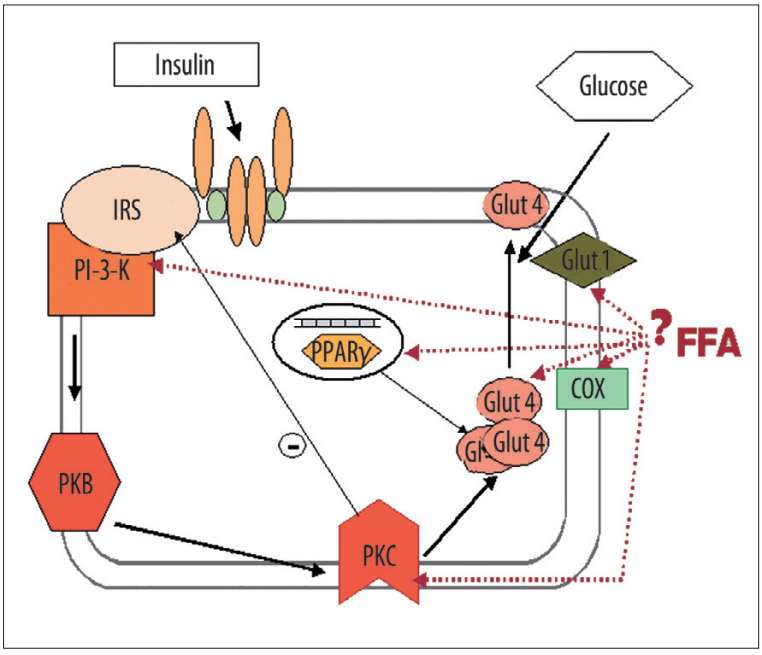

Figure 5. Possible role of fatty acids in the insulin signalling pathway: Insulin reacts with its receptor and causes autophosphorylation and tyrosine phosphorylation of the insulin receptor substrate (IRS). This, in turn, activates phosphatidylinositol-3 kinase (PI3K) and, further downstream, protein kinases B and C (PKB and PKC). PKC promotes the translocation of GLUT4 from cytoplasmic vesicles to the cell membrane where the latter promotes uptake of glucose. Fatty acids may act on this pathway via prostaglandin formation and activation of PI3K or PKC. Activated PKC may also cause serine/threonine phosphorylation of IRS, thus preventing normal tyrosine phosphorylation, thus attenuating the insulin signal. Alternatively, fatty acids may activate GLUT1 independently of insulin. Lastly, fatty acids can modulate gene expression, probably via the PPARγ transcription factor.

chidonate-rich fungal oil or fish oil in mice can influence the expression of different sets of genes of major eukaryotic lipid metabolism transcription factors.

Interestingly, the *trans*-10, *cis*-12 isomer of conjugated linoleic acid has antiobesogenic metabolic effects [49] but, surprisingly, downregulates PPARγ action in adipocytes, leading to negative effects on insulin sensitivity. The differential interaction of individual fatty acids with PPARγ is a highly complex phenomenon and currently under intense investigation. Contradicting evidence may be ascribed to differing experimental models, and, at least partly, to polymorphism of the PPARγ-1 and -2 genes [101]. Finally, in addition to GLUT4, fatty acids can also impact on the transcription of the mitochondrial UCPs via PPAR [67,102] thus influencing obesity, and, indirectly, insulin sensitivity.

Conclusions

The interaction between lipid and carbohydrate metabolism has long been an area of great interest and research. The classical theory forwarded by Randle and coworkers in 1963 [103] stated that increased fatty acid breakdown could lead to decreased glucose oxidation via the effects of acetyl-CoA on pyruvate dehydrogenase. This concept has been superseded by *in vivo* studies [33,34] that have shown that increasing free fatty acid concentrations by infusion can inhibit the first step leading to glucose oxidation, that is, insulin-stimulated cellular glucose uptake.

Similar to the effects of free fatty acids, the dietary fatty acid profile also impacts on insulin sensitivity [5,9]. Multiple mechanisms may be involved in these effects: amongst the most exiting new possibilities are the polymorphisms noted in the PPARγ-2 gene that could explain genetic predisposition to metabolic syndrome [101] and also the possible linking of the immune system to fat-induced insulin resistance via IkB kinase/nuclear factor-kappa B pathway [104].

Extreme caution is advised when following or exploiting modern fast food dietary trends: the increased use of saturated and especially *trans*-fatty acids in food processing is rapidly leading to an avalanche of insulin resistance coupled with type 2 diabetes mellitus in western countries and those adopting a western lifestyle. This has been well illustrated by a recent study in India [105] where increased consumption of vanaspati, a fat rich in *trans*-fatty acids, is of concern: feeding rats vanaspati leads to adipocyte membrane changes and insulin resistance.

The importance of a balanced ratio of omega-6 to omega-3 intake, as in the ancient Paleolithic diet, was recently tested in the Lyon Heart Study [106]. This study was a prospective, randomized, single-blinded secondary prevention trial, which compared the effects of a modified Crete diet, enriched with ALA (ratio of omega-6/3, 4:1), low in saturated fat, very low in trans fat and high in vitamin C and E, to that of a Step I American Heart Association Diet in the secondary prevention of coronary events and death. The American Heart Association does not distinguish between omega-6 and omega-3 fatty acids, and ignores the detrimental effects of trans fatty acids, while proposing a prudent diet low in fat and high in carbohydrates. The modified Crete diet clearly illustrated reduced risk for coronary heart disease and cancer. Western diets have over the years become depleted in omega-3 fatty acids, while the widespread use of inexpensive vegetable oils, rich in omega-6's, have resulted in very unfavourable ratios of omega-6: omega-3 of 20:1 and higher. It may well be wise for us to return to the hunter-gatherer diet of our ancestors or the suggested Mediterranean (Crete) type diet [106,107] that contains less saturated and trans-fatty acids, and more polyunsaturated fatty acids with a much improved omega-6/omega-3 ratio [107].

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