Turkish Journal of Endocrinology and Metabolism, (2001) 1 : 1-16 **ORIGINAL ARTICLE**

Energy Dense High-Carbohydrate and Low-Fat Diets Are the Reason For the Epidemic of Metabolic Syndrome -Novel Approach to Etiopathogenesis of Metabolic Syndrome-

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In this study, the etiopathogenesis of metabolic syndrome parameters was discussed and it was pointed out that malonyl-CoA, a lipogenic glucose metabolite, might be responsible for a common mechanism in hyperinsulinemia and insulin resistance, triglyceride synthesis and storage, cholesterol synthesis and the development of ischemic heart disease.

Key words: Malonyl-CoA, metabolic syndrome, apoptosis

With obesity reaching epidemic dimensions, its association with degenerative metabolic diseases, especially diabetes mellitus and atherosclerosis, has been clearly established (1). Research shows that approximately 20% of the population in United States are obese (2) and obesity has become an alarming factor in the adolescent age group (3).

Because fatty foods are rich in calories and the role of cholesterol in the pathogenesis of atherosclerosis has become evident, diets having carbohydrates as the main component and having low cholesterol and fat remain as a major approach for the treatment of atherosclerotic disease (4, 5). In the last two decades when this type of diet has been strictly used, the prevalence of obesity and type 2 diabetes has increased whereas no decrease in atherosclerotic disorders has been detected (6).

Competition of glucose and fatty acids as fuel and the Randle Hypothesis

According to Randle who performed his investigations on heart muscle (7), the fatty acid present in the medium is the determinant of fuel use in the cell (8, 9). In other words, while the fatty acid present is oxidized, it hinders oxidation of glucose (10). In this hypothesis summarized in Figure 1, an increase in fatty acids or ketone bodies leads to accumulation of acetyl-CoA and NADH which results in inhibition of glucose metabolism at the pyruvate dehydrogenase (PDH) level (11).

Thus, glucose metabolism is inhibited at two important steps (12). At the first step, the increased cytoplasmic citrate concentration inhibits phosphofructokinase. This leads to accumulation of glucose-6-phosphate because it is not used and this results in inhibition of hexokinase. Thus, the access of glucose into the cell (uptake) is hindered (13) (Figure 1). At the second step, pyruvate dehydrogenase enzyme is inhibited as a result of activation of pyruvate dehydrogenase kinase and this prevents the entry of pyruvate into the oxidative metabolism leading to impairment of the oxidation of glucose (12, 13) (Figure 1). This hypothesis advocated by many authors forms the basis of the mechanism that lies beneath the argument which is still valid at the present time that excessive fatty acids and nutrition rich in fat lead to insulin resistance. However, in keeping with the principles stated below currently it is accepted more widely that glucose is the molecule responsible for the partitioning of fuel in the cell (14, 15).

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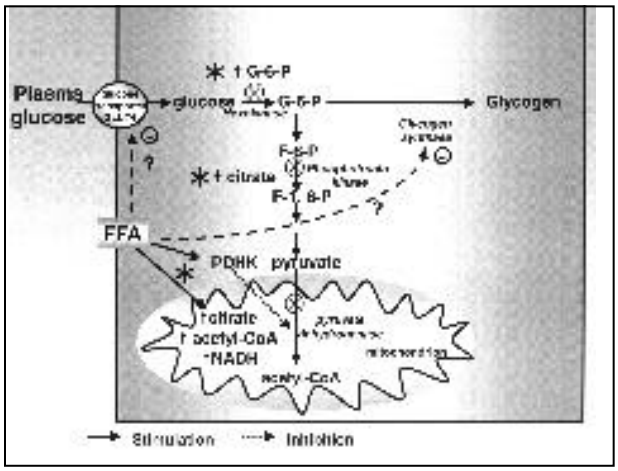

Figure 1. Randle hypothesis: according to Randle, potential sites (indicated with the symbol *) of free fatty acids (FFA) action on insulin mediated metabolism. PDHK: pyruvate dehydrogenase kinase, G-6-P: glucose-6-phosphate, F-6-P: fructose-6-phosphate, F-1,6-P: fructose 1,6 diphosphate. Dotted arrows denote inhibition (See reference 11 for further details).

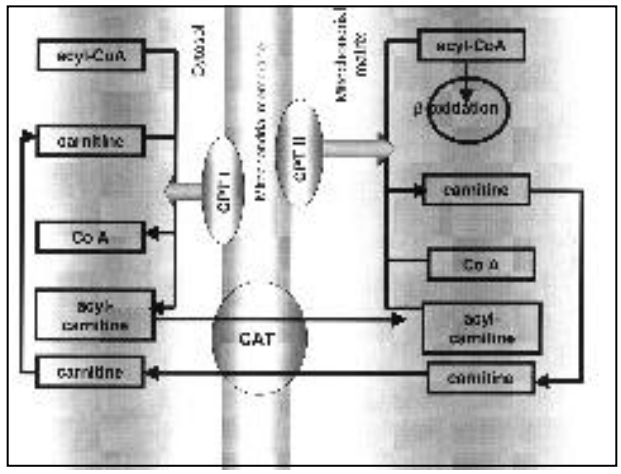

Figure 2. Scheme of long chain fatty acid transportation to mitochondria and carnitine shuttle, CPT: carnitine palmitoyltransferase, CAT: carnitine acylcarnitine transporter.

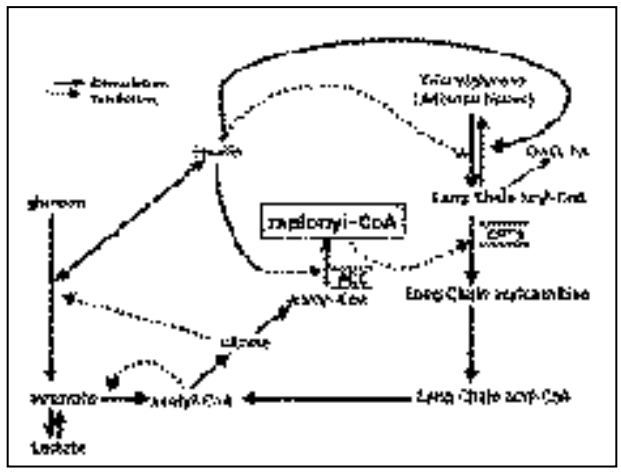

Figure 3. Coordinated utilization of glucose and fatty acids and importance of malonyl-CoA. ACC: acetyl-CoA carboxylase, CPT: carnitine palmitoyltransferase, DAG: diacylglycerol, PA: phosphatidic acid. Dotted arrows denote inhibition (Adapted from reference 16).

Glucose, fatty acid and malonyl-CoA

In order for long chain fatty acid-CoA (LCFA-CoA) in the cell cytosol to be β-oxidized in the mitochondria (16), carnitin palmitoyltransferase 1 (CPT1) enzyme located in the outer membrane of the mitochondria is needed (17). LCFAs carried to the cell mitochondria after joining with carnitin are separated from the carnitin by means of the CPT2 enzyme located in the inner membrane of the mitochondria. Then, they go through β-oxidation via esterification with CoA (25). The freed carnitin joins the "carnitin shuttle" to be used again (18) (Figure 2).

Malonyl-CoA, an intermediary product in de novo lipogenesis of carbohydrates, is yielded from acetyl-CoA by means of the acetyl-CoA carboxylase (ACC) enzyme (18-20) (Figure 3). The yielded malonyl-CoA constitutes an important stage in de novo lipid synthesis from carbohydrates (21). By means of the fatty acid synthase (FAS) enzyme, 7 malonyl-CoA is joined with an acetyl-CoA to form palmitic acid (22). Palmitic acid goes through esterification with glycerol in the endoplasmic reticulum of the the cell and is stored after being converted to triacylglycerole (=triglycerid) (23). The inhibitory effects of malonyl-CoA over CPT1 were established in the studies done by DJ McGarry. The metabolic intermediary step for malonyl-CoA synthesis is very important and the ACC enzyme has a rate determining feature (24, 25) (Figure 3). Thus, glucose in excess of the energy need of the cell leaves the mitochondria as citrate and enters the cell cytoplasm where it is used in fatty acid synthesis as substitute fuel by means of malonyl-CoA (26). It also prevents the entry of fatty acids (fats mostly ingested with food) into the mitochondria to be oxidized by means of the same metabolite (malonyl-CoA) (27, 28) (Figure 4).

To summarize the explanations given above in one sentence, it can be stated that malonyl-CoA is a versatile intracellular signal molecule (=intracellular signal of plenty) (29).

The fate of fats not oxidized in the cell

Following a mixed diet predominantly comprising carbohydrates, the glucose in excess of the need is stored as reserve cell fuel in the form of triglycerides by means of de novo lipogenesis (DNL) (30, 31). Fats not entering the mitochondria to generate energy through oxidation are accumulated in the cell in the form of LCFA-CoA and its further metabolic products such as phosphatidic acid (PA) and diacylglycerol (DAG) (32, 33). These three molecules of fat metabolites keep the cell stimulated for an unusually prolonged time via causing alterations in the membrane and ions responsible for maintaining cell integrity and by commencing enzyme activations (phosphorylation/ dephosphoryation) (34) (Figure 4).

If the fat mass accumulated in the cell as a result of chronic carbohydrate excess can not be controlled through an increase in the compensatory function of the mechanisms protecting the homeostasis of the organism, cell death ensues as a result of lipoapoptosis (35, 36). The functioning of the mechanisms outlined in Figure 5, for the details of which the mentioned references will be consulted, and the loss of the cell occurring through apoptosis mediated by ceramide (37), a fatty acid metabolite, cause function failures in organs with time (lipotoxicity hypothesis) (38).

This is the most tangible picture of the basic functioning of the nonadipocyter cell type generated

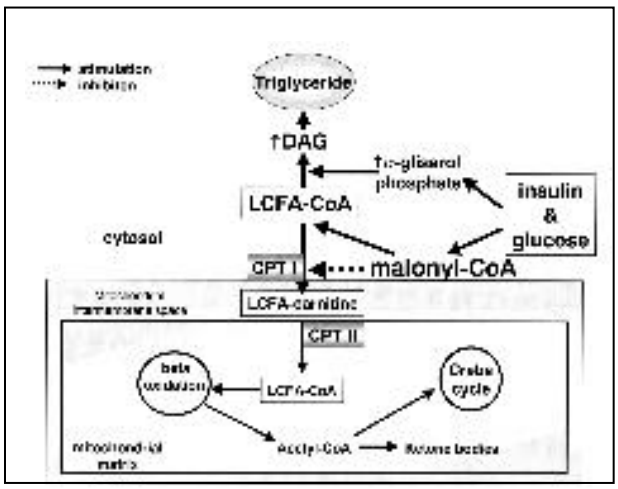

Figure 4. Interrelation between glucose & insulin and long chain fatty acid (LCFA) disposition. DAG: diacylglycerol, CPT: carnitin palmitoyltransferase. Dotted arrows denote inhibition (See references 16 and 105).

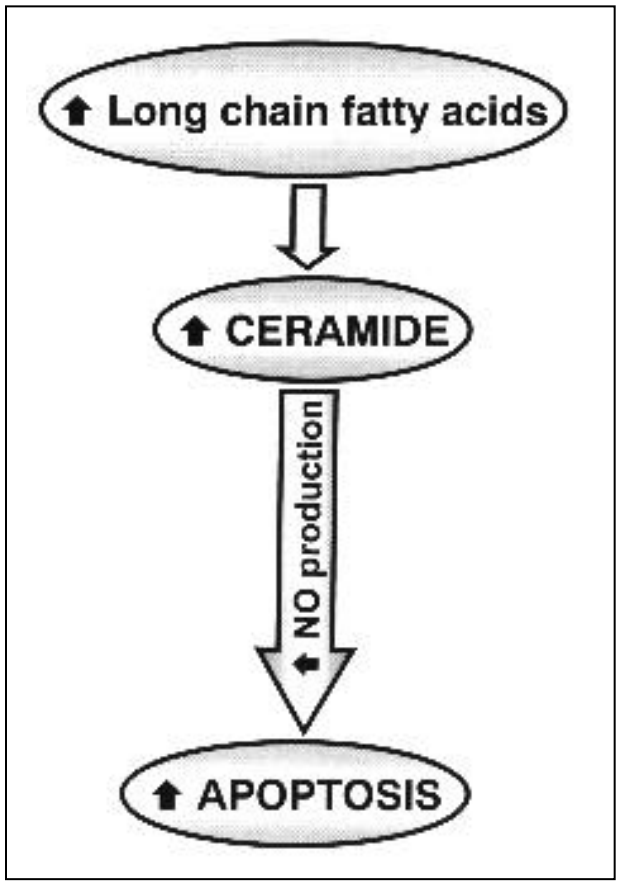

Figure 5. Proposed scheme for regulation of apoptosis by long chain fatty acids. NO: nitric oxide (See references 37and 73 for further details).

as a result of a chronic diet rich in carbohydrates. Now we are going to apply this to various organs and try to understand how small biochemical functioning differences cause important alterations leading to the physiopathologic features of obesity and metabolic syndrome.

The fat organ and the adipocyter system

The fat organ (39) is of pivotal importance in the formation of metabolic syndrome. In the course of the evolutionary process, fat cells have acquired the ability to store excess energy as triglyceride in a virtually unlimited manner (40). Two basic benefits are obtained this way. First of all, the organism has gained a great deal of flexibility and freedom as a result of being relieved from the limitations of continuous fuel replacement. Secondly, very limited amounts of fat are found in the nonadipocyter system cells to meet urgent needs (41). Amounts of fat exceeding this can cause toxication by mechanisms

which were explained briefly above. Thus, fat tissue prevents the accumulation of fat in the nonadipocyter system by gathering the excess fat in its own body (41).

The fat tissue has special equipment for DNL (42) (Figure 6). The genetic system coding the glycolytic and lipogenic enzymes, especially pyruvate kinase (PK), ACC, malic enzyme (ME), FAS, and glyceraldehyde phosphate dehydrogenase (GAPD), is quite well developed (23). Glucose alone or fortified with insulin stimulates the expression of these genes and the synthesis of enzyme proteins (43, 44). DNL has such a strict controlling system that glucose and/or insulin also activates transcription factors such as Peroxisome Proliferator Activated Receptor γ (PPAR γ) (45) and Sterol Regulatory Element Binding Protein 1a (SREBP1a) (46, 47). Thus, the lipogenetic and storing functions of fat tissue can operate extremely well against all kinds of difficulties. In the mentioned references, the very clear molecular mechanisms of these glucose and insulin mediated arrangements are elucidated comprehensively (21-23, 25, 40). Insulin also stimulates the transition of glucose carriers (GLUT4) from the cytosol to the membrane of fat cells (48). At the end of these procedures carbohydrate excess resulting from diet, glucose that could be harmful for the nonadipocyter system is transported to fat cells (49). The selective insulin resistance generated in the muscle in particular prepares the setting for obesity and the other metabolic syndrome parameters through increasing glucose flow into the fat tissue as a result of performing novel arrangements in the distribution of substrates (50).

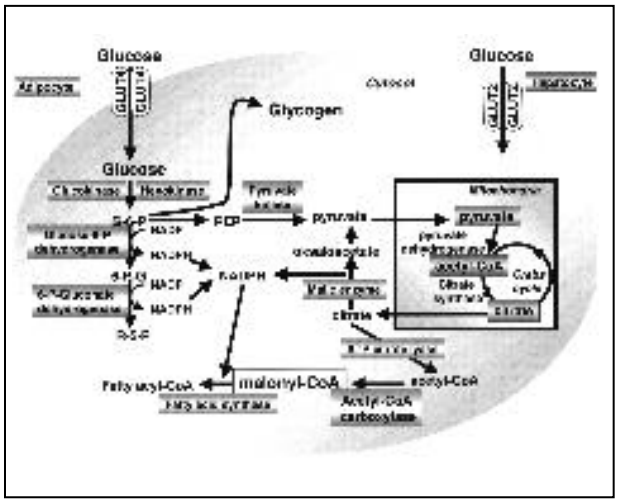

Figure 6. Scheme of the biochemical pathways of lipogenesis from glucose in the liver and adipose tissue. G6P: glucose-6-phosphate, PEP: phospho enol pyruvate, 6-P-G: 6 phospho gluconate, R5P: ribosyl-5-phosphate (See references 22 and 38 for further details).

Fat cells, which start storing lipid, also start the synthesis and secretion of leptin as a protective first aid signal! for the nonadipocyter cells that encounter this situation unprepared (51). Leptin tries to prevent the accumulation of lipid in the cell by activating enzyme expressions (52) that increase fatty acid oxidation, which leads to rectification of the malonyl-CoA mediated pathologic mechanisms (53). Namely, fatty acids while storing the energy excess originating from a mixed diet rich in carbohydrates, to use when there is a need produce protective control mechanisms to prevent accumulation of fat that could cause the impairment of physiologic functions of other system cells (54).

Malonyl-CoA, pancreatic β-cells, and hyperinsulinemia

In normal pancreatic β-cells the FAS system is weak with respect to the well-developed ACC enzyme genetic structure (29, 55). Hence, in the case of glucose excess malonyl-CoA synthesis will increase with the hyperactivation of ACC enzyme (56, 57) whereas FAS mediated fatty acid production, which is the main pathway for the elimination of malonyl- CoA will be inadequate (58). The result is a marked increase in the cytosolic malonyl- CoA concentration (59). If we apply figure 4 to b-cell, the increase in malonyl- CoA will cause the accumulation of non-oxidized fatty acid metabolites (LCFA-CoA, PA and DAG) as a result of the inhibition of the CPT1 enzyme (29, 34). Thus, membrane K^{+}_{ATP} channels close (60, 61), the amount of cytosolic Ca^{+2} increases and the hyper-polarized cell secretes insulin (29, 62) (Figure 7). Chronic and misusing of this mechanism causes to increased insulin secretion that best explains the hyperinsulinemia of metabolic syndrome (63). In fact, β-cell functions as a sensor in the case of glucose excess, and increases glucose entry into the fat and muscle tissues susceptible to insulin via hyperinsulinemia, providing a compensatory elimination (64).

The well-known anabolic effects of insulin (65) increase fat storage by means of promoting lipo-

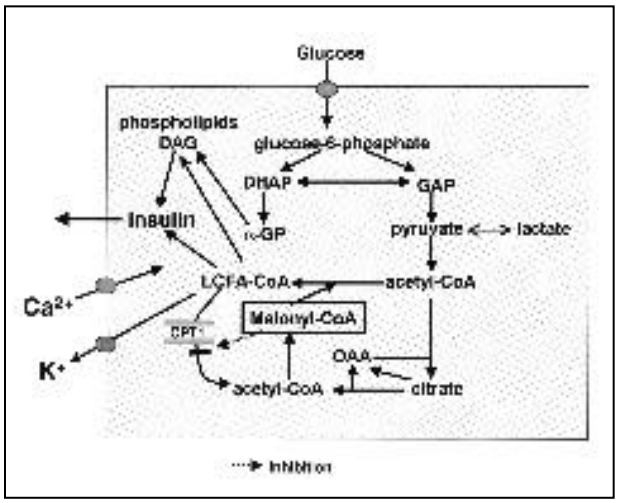

Figure 7. Proposed scheme of the biochemical reactions necessary for insulin secretion in pancreatic β-cells. CPT: canitine palmitoyltransferase, DAG: diacylglycerol, DHAP: dihydroxy acetone phopsphate, α-GP: α glycerol-3-phosphate, GAP: glyceraldehyte-3-phosphate, OAA: oxalo acetic acid. Dotted arrows denote inhibition (Adapted from reference 66).

genesis in fat cells (66). Leptin secreted as a response to fat storage in the adipocyte (41, 67) induces the PPARα transcription factor in pancreatic β-cells leading to the increase in genetic expressions of fatty acid oxidation enzymes, especially CPT1 (68, 69) (Figure 8). Thus, the impaired fatty acid oxidation as a result of the increase in malonyl-CoA in

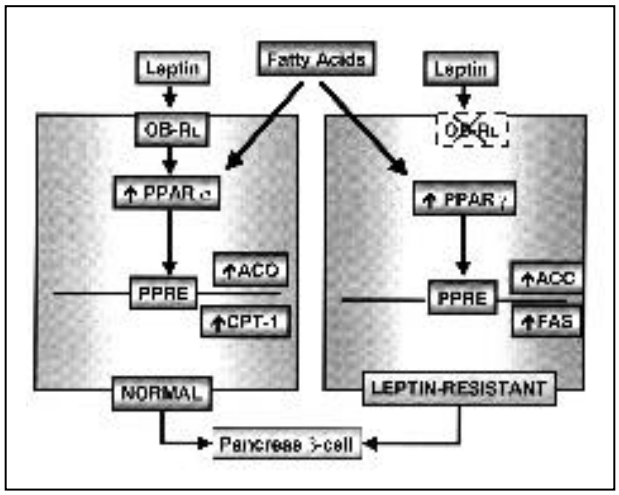

Figure 8. Influence of leptin in nonadipocyter system in normal and leptin resistant state. PPARα: peroxisome proliferator activated receptorα, ACO: acyl-CoA oxidase, CPT-1: carnitine palmitoyltransferase-1, PPARγ: peroxisome proliferator activated receptor γ, ACC: acetyl-CoA carboxylase, FAS: fatty acid synthase, PPRE: PPAR response element, OB-RL: long form of leptin receptor (Adapted from and see reference 37 for further details).

physiologic temporary glucose loading is reorganized (70). However, in chronic glucose loading the malonyl-CoA increase in the cell is prolonged. This situation prevents fatty acid oxidation and causes the accumulation of fatty acid metabolites mentioned above and this can lead to leptin resistance by means of possible membrane and leptin receptor alterations (71, 72). As a result of these reactions shown in Figure 8, fatty acid metabolites inside the cell form endogenous ligands for PPARγ (73) and enhance the transcription of the genes controlling ACC and the FAS enzyme which is expressed weakly in β-cell (86). The net result is triglyceride storage in β-cell (74). After a threshold value in the accumulation of triglyceride in β-cell, lipoapoptosis as explained in the introduction ensues (35, 36) (Figure 5). Apoptotic pancreatic β-cell loss can lead to type 2 diabetes mellitus in the course of time (75, 76).

Glucose excess and the liver

In the liver, which is a lipogenic organ, glucose can readily enter the cell with the glucose transporters (GLUT2) (21, 77) located in the membrane. Insulin accelerates the phosphorylation of glucose as glucose-6-phosphate (G6P) (78, 79) through enhancing the glycokinase gene expression (80). Successively, G6P enhances the expression of the genes controlling lipogenic enzymes and their protein synthesis (21). Moreover, with the activation of glucose and insulin mediated PPARγ and SREBP1 transcription factors fatty acid and triglyceride synthesis increases via DNL, (45, 81) and fatty acid oxidation decreases with diminished PPARα (82). The predominant fat following endogenous DNL is palmitic acid which is a saturated fatty acid (83). The generated fat is again converted to VLDL by means of insulin (84) and is transported to be stored in the adipose tissue (85). This causes an increase in triglyceride secretion and an elevated blood triglyceride level (86). In the case of persistence of energy excess, the clinical presentation of hepatic steatosis ensues and this phenomenon is usually encountered in obesity and metabolic syndrome and is often mistaken as being benign (87, 88). This increase in fat in hepatocytes causes lipoapoptosis with mechanisms similar to those seen in pancreatic β-cells (Figure 5), and can lead to hepatic failure in the long term (89, 90).

The liver is the place where cholesterol synthesis occurs which is another important atherogenic lipid (91). As a result of diets rich in carbohydrates, the acetyl-CoA exceeding the need accumulates in the hepatocyte cytoplasm as cytosolic citrate. Citrate is first converted into acetyl-CoA and then forms triglycerides by entering the lipogenic pathway over malonyl-CoA (26). Acetyl-CoA and especially malonyl-CoA (92, 93) are also substrates necessary for cholesterol synthesis (Figure 9). This flow from citrate towards cholesterol is associated with the feeding status of the subject (94).

With today's favorable diets containing very low cholesterol, little fat, and plenty of carbohydrates, (95) the immature SREBP2 embedded in the endoplasmic reticulum, which provides transcriptive control of the genes coding enzymes responsible for cholesterol synthesis, is activated (96, 97) and converted to the mature or nuclear form named nSREBP2 (98). SREBP2 and SREBP1 are members of the same family that are subject to different genetic control and responsible for different metabolic pathways by means of different protein synthesis (96, 97). It is now clear that the enzymes SREBP2 controls are 3-hydroxy-3-metylglutaryl CoA (HMG CoA) reductase, HMG CoA synthase, farnesyl diphosphate synthase, and squalene synthase (99). This system is subject to feedback control and the endogenous cholesterol synthesis continues until the cholesterol level inside the cell reaches a threshold

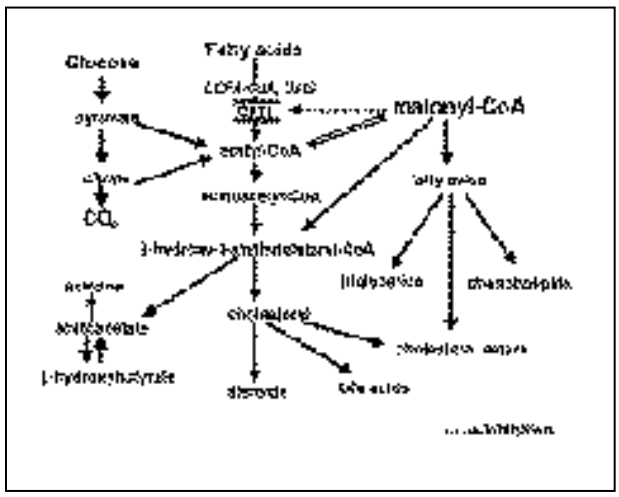

Figure 9. Fat and cholesterol synthesis from carbohydrates and fatty acids, and importance of malonyl-CoA. CPT: carnitine palmitoyltransferase, DAG: diacylglycerol, LCFA: long chain fatty acid. Dotted arrows denote inhibition.

value (100, 101). An interesting point here is that the low cholesterol level inside the cell that triggers the increase in cholesterol synthesis also upregulates ACC mRNA (102). Namely, diminishing the cholesterol in the diet causes the increase of endogenous cholesterol synthesis and ACC, the rate determining enzyme for fatty acid synthesis, leading to an increase in malonyl-CoA (102).

SREBP1 causes an increase in LDL receptors at the hepatocyte surface by means of stimulating the transcription of LDL receptor genes together with genes functioning in fatty acid synthesis (103). Cholesterol that increases as a result of the mechanisms described above is secreted outside hepatocyte in the form of LDL and is transported back into hepatocyte by LDL receptors increased in number (104, 105). Hence, blood cholesterol and LDL levels do not elevate very much for such a dislipidemic situation (106). However, in metabolic syndrome, LDL particles are small, dense, and more sensitive to oxidation and therefore, have a more atherogenic character (107).

Carbohydrate excess, skeletal muscle and insulin resistance

Important alterations take place also in skeletal muscle tissue where fuel use is the most important in the case of diets chronically rich in carbohydrates (108). Acetyl-CoA accumulates in the cytoplasm as citrate following the generation of ATP exceeding the cell need as a result of glucose excess taking the glycolytic pathway in the tricarboxylic acid cycle (109). Phosphofructokinase (PFK), the rate determining enzyme in the glycolytic pathway, is inhibited in the case of citrate excess as demonstrated by the refined studies of Ruderman and co-workers (110). With the inhibition of PFK catalyzing the conversion of fructose 6 phosphate to fructose 1,6 diphosphate an accumulation of substrates prior to this step ensues and with the increase of G6P part of the glucose shifts to the glycogen synthesis (111) (Figure 1). With the filling of the limited glycogen stores, G6P that cannot feed the glycolytic pathway accumulates and inhibits the hexokinase (112). This means failure of insulin to insert glucose into the muscle cell; briefly, insulin resistance.

CPT1 protein in the skeletal muscle and the liver are different. The isoform in the muscle is more

sensitive to malonyl-CoA inhibition (113). A small portion of the malonyl-CoA present can be effective in the inhibition of CPT1 (113, 114). High concentrations of malonyl-CoA in the presence of insulin and glucose limit the transition of LCFA-CoA into the mitochondria and increase the amount in the cytosol and the conversion to glycerolipids (in many insulin resistance conditions, the amounts of triglyceride, diacylglycerol, and LCFA-CoA are increased)114 (Figure 4).

The effects of the decrease in malonyl-CoA concentrations on lipid metabolites and insulin resistance have attracced little attention. The acute decrease in skeletal muscle malonyl-CoA level with exercise enhances the response and sensitivity to the stimulating characteristic of insulin on glucose transport and glycogen synthesis (115). The accumulation of cytosolic LCFA-CoA is the common feature in insulin resistance whether originating from malonyl-CoA or free fatty acids or especially in association with the increase in both of them (116) (Figure 4). The accumulation of LCFA-CoA causes one or more protein kinase (PKC) activations by increasing the concentrations of DAG, phosphatidic acid, and triglyceride (117). PKCs inhibit glycogen synthase and insulin receptor through phosphorylation (118) (Figure 10). With the increase in hexosamine synthesis, the amount of LCFA-CoA is responsible in another manner for insulin resistance developing in muscle and fat tissue during the hyperglycemia period (119).

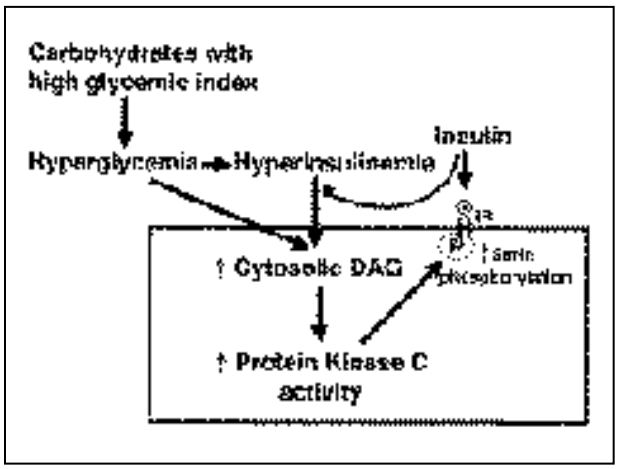

Figure 10. Proposed mechanism for glucose-induced phosphorylation of the insulin receptor. DAG: diacylglycerol, IR: insulin receptor (Adapted from reference 109).

Let us consider the issue of malonyl-CoA causing insulin resistance over skeletal muscle from another point of view. The favorable effects of physical activity on insulin resistance are well known (120, 121). AMP amount increases with the use of ATP following exercise. The increase in the AMP/ATP ratio causes the stimulation of AMP activated protein kinase (AMPK) (120, 122). AMPK phosphorylates ACC at least at three serin residues (122, 123). Phosphorylation engenders marked ACC inactivation, and reduced sensitivity of the enzyme to the allosteric activator effect of citrate (124). The ACC isosymes of the liver, fat tissue, heart and skeletal muscle are identical and are influenced by AMPK phosphorylation (137). Even the minimal changes in ATP concentrations will influence AMP and therefore the AMPK enzyme (125) (Figure 11). As a result, the AMPK-ACC connection functions as another sensor-effector that informs the cell of the changes in adenylate load (126). These changes in skeletal and heart muscle are actually compensatory; they give an alarm in the case of decreased ATP and enhance the generation of ATP. AMPK activation in liver not only causes an increase in fatty acid oxidation through the mechanism connected with malonyl-CoA, but also it reduces the rate of fatty acid and cholesterol biosynthesis (127). Besides, AMPK regulates similar adaptive changes in muscle during the periods of hypoxia, ischemia and exercise

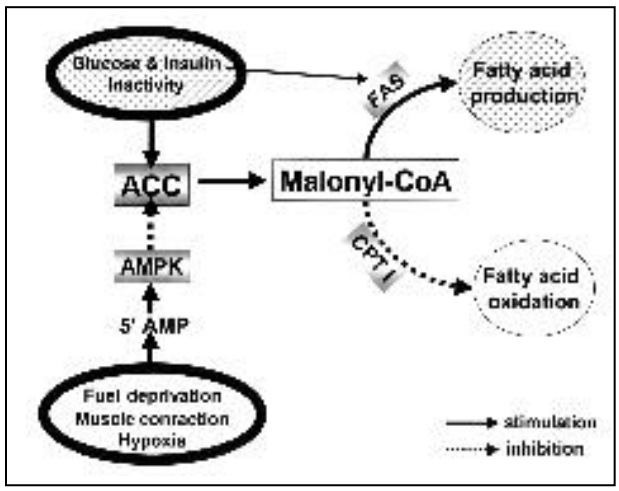

Figure 11. Interrelation between fatty acid production and oxidation over malonyl-CoA in relation to glucose availibility and energy expenditure. ACC: Acetyl-CoA carboxylase, AMPK: AMP activated protein kinase, CPT: carnitine palmitoyltransferase, FAS: fatty acid synthase. Dotted arrows denote inhibition (See references 100, 105, and 116 for further details).

(128). In the case of glucose excess, ATP increase and AMP decrease cause the inhibition of the system dependent on AMPK (120, 126, 128). As a result of the events, the details of which can be found in the mentioned references pertaining to the molecular mechanisms, glucose excess as fuel and a sedentary life can cause insulin resistance again over ACC and malonyl-CoA via another important mediator route120 (Figure 11).

Glucose excess and the heart

Fats are the basic fuels that meet the cardiac energy need (129). The heart is an organ with the characteristic of being able to burn in different fuels the best way at the same time (*omnivorous*) (130). At the cardiomyocyte membrane, there is an interesting situation pertaining to the glucose transporters. The real transporter is the GLUT4 which is also found in fat cells and is dependent on insulin (131). Moreover, normal cardiomyocyte also possesses GLUT1 expression which is found more commonly in the fetal myocard cell and is not dependent on insulin and to a lesser extent GLUT3 expression (132). Thus, via these different transporters, glucose is provided for the cell at the highest rate.

The pathway that proceeds to glycogen synthesis over G6P and the glycogen cycle are very active in the cardiomyocyte (133). Glycogen constitutes 3% of the cardiomyocyte cell volume in adults and 32% in the newborn (134). In contrast with the liver and skeletal muscle, heart muscle continues glycogen synthesis while fasting (135). When needed, glucose is obtained by means of glycogen undergoing glycogenolysis with the aid of glycogen phosphorylase enzyme (136). Epinephrine and glucagon are potent stimulators of glycogen phosphorylase (137). With these explanations, it has been attempted to emphasize that the cell makes the necessary arrangements to ensure a strong flow of glucose, one of the fuels, into cardiomyocyte.

During rest and normal exercise, the predominant energy source in the mammal heart is LCFAs (138). The CPT1 enzyme needs to be activated so that LCFAs can enter the mitochondria and be oxidized in the heart (139). In cardiomyocyte, CPT1 is subject to a strict malonyl-CoA inhibition (140). The increase in the amount of malonyl-CoA markedly prevents the oxidation of fatty acids (141). Because the expression of the FAS enzyme is weak in the cardiomyocyte, (140, 142). following a compensatory increase in the amount of malonyl-CoA decarboxylase, another enzyme responsible for the degradation of malonyl-CoA, provides adequate activation of CPT1 by means of reducing cytosolic malonyl-CoA level (143). However, in the case of excessive malonyl-CoA production the elimination capacity of this system cannot suffice (144). Consequently, reduction in the oxidation of fatty acids and the accumulation of cytosolic LCFA-CoA can cause signaling defects and alterations in the ion equilibrium inside the cell leading to cardiac rhythm and function disorders (145) (Figure 12).

During the fetal period, glucose and lactate are used as the main energy sources (146). Following birth and during the postnatal period myocardial energy is obtained via processing LCFAs with β-oxidation. In the normal adult heart, mitochondrial fatty acid oxidation is responsible for most of the ATP production (147). Childhood cardiomyopathy and sudden deaths occur by the accumulation of the intermediary products of LCFAs in cardiomyocyte (146). Reduction in energy stores as a result of failure in the oxidation of fatty acids is caused by a genetic error in the enzymes of mitochondrial fatty acid oxidation (FAO). Under these circumstances, the importance of the members of the nuclear receptor

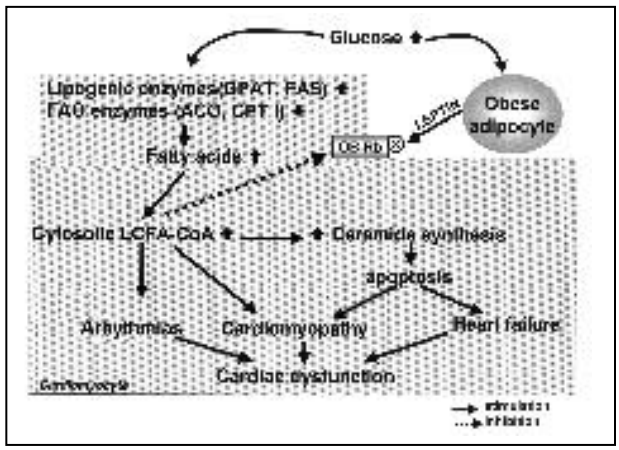

Figure 12. Proposed mechanisms leading to cardiac dysfunction in carbohydrate excess. ACO: acteyl-CoA oxidase, CPT: carnitine palmitoyltransferase, FAO: fatty acid oxidation, FAS: fatty acid synthase, GPAT: glycerol-3-phosphate acyl transferase, LCFA: long chain fatty acid, OB-Rb: long form of leptin receptor. Dotted arrows denote inhibition (See references 130, 131, and 134 for further details).

family becomes apparent in the transcriptional control of the genes responsible for coding cardiac FAO enzymes (148).

PPARα activates the transcription of FAO enzyme genes (149). PPARα inhibition as a result of glucose increase causes reduction of mitochondrial FAO enzymes (145, 149). Thus, the accumulation of the intermediary products of LCFAs prepares the setting for ventricular rhythm disorders similar to those seen in myocardial ischemia and in patients with cardiomyopathy originating from congenital FAO errors (145).

Apoptosis developing from the activation of the ceramide pathway, presented as a general principle in the introduction, as a result of the accumulation of triglyceride and the other fatty acid metabolites inside the cell is also valid for cardiomyocytes (150). Apoptotic cardiomyopathy and heart failure triggered by the accumulating palmitate with the inhibition of CPT1 can ensue (151) (Figure 12).

Diets rich in carbohydrates and atherosclerosis

As a result of chronic diets rich in carbohydrates and poor in fats (DRCPF), the setting for atherosclerosis is being prepared with the changes described above in adipocyte, pancreatic β-cell, hepatocyte, skeletal muscle cell, and cardiomyocytes. The basic parameters of the metabolic syndrome such as hyperinsulinemia, an increase in the synthesis of fatty acids and cholesterol by DNL causing atherogenic dislipidemia, and insulin resistance take place. Obese adipocyte secretes angiotensinogen, (152) atherosclerotic coagulative factors and factors that increase vascular reactivity such as angiotensin (AT) II, (153) plasminogen activator inhibitor 1 (PAI1), (154) and tissue factor (155). Insulin prepares the infrastructure for hypertension and atherosclerosis via retaining salt and water, causing the activation of the sympathetic nervous system, (156) and enhancing vascular tonus as the vascular growth factor (157). Moreover, insulin causes the increase of the vascular AT1 receptor gene expression (upregulation) by means of post-transcriptional mechanisms (158). In addition to vascular reactivity increase, vasoconstriction and the activation of coagulation pathways to atherogenic dislipidemia engenders hypertension and premature atherosclerosis. The details of this subject matter can be found in the literature (159).

Diets rich in carbohydrates and cancer

Histologically, the expression of enzymes responsible for fat synthesis is low in breast tissue (160). Marked increases of especially FAS and the other lipogenic pathway enzymes are detected in cancers of the breast in particular and of the colon, prostate, thyroid, and endometrium (160-163). Two distinct mechanisms can be proposed pertaining to this topic. Chronic active involvement of the lipogenic pathway can cause cellular signaling alterations described above and adverse genetic arrangements done by cytosolic fat metabolites (160). Another argument is that the lipogenic pathway is activated in the abundance of glucose coming as fuel to the cancer tissue with increased vascularity (160). The abundance of fuel that will maintain lipogenesis in both pathways seems to be important in the development of cancer. Besides, it is thought that insulin, a cellular growth factor, could trigger neoplasia alone or in association with insulin receptor alterations in high insulin levels (164).

It has become clear that the use of FAS inhibitors shows cytotoxic effects in breast cancer (165). However, the continuation of cytotoxicity when fatty acid supply is provided together with FAS inhibitors has established the fact that the effect brought about is not associated with the prevention of fatty acid synthesis. With the use of FAS inhibitors, accumulation of malonyl-CoA, the substrate in the previous step, will occur. It has been clarified that the accumulated malonyl-CoA amount is responsible for the cytotoxicity by detecting the reduction in cytotoxicity when the inhibitor of ACC, the enzyme responsible for the production of malonyl-CoA, is given together with FAS inhibitor (165). That is, malonyl-CoA accumulating with increased synthesis in the abundance of glucose acts as a toxin that could even cause cell death unless its concentration is diminished inside the cell by means of further metabolizing.

Certain arrangements should be made in order to prevent malonyl-CoA from accumulating and showing toxic effects inside cells that encounter glucose chronically exceeding the metabolic need. As a result of the mechanisms that are widely explained above, glucose causes overexpression of various molecules exceeding the need, FAS being

the most conspicuous one. Glucose achieves this through its direct effects on the genetic material and by exerting chronic stimulating effects with the mediation of insulin and transcription factors. Thus, it can be speculated that chronic stimulations caused by glucose excess as fuel can engender neoplastic transformation in cell types that have a genetic predisposition.

Results

1. DRCPF causes increased fat synthesis and storage by means of substrate abundance in lipogenic organs, stimulation of essential enzymes for metabolic pathways, and by providing genetic arrangements (=obesity).
2. In DRCPF, with the biochemical inhibition occurring in the oxidation of fats taken in small amounts in mixed diets, this important fuel increases fat storage instead of giving energy.
3. Fatty acids, the oxidation of which is prevented by DRCPF, cause an increase in the generation of metabolites such as DAG and PA in the cell and these metabolites cause insulin and leptin receptor resistance by means of impairing signal transport as a result of interactions with molecules (such as protein kinase C, JAK, STAT) mediating message delivery inside the cell.
4. As a result of the difficulty of glucose access into the cell originating from insulin resistance encountered following DRCPF, substrate deficiency will ensue consequently inside the cell to be oxidized although there is plenty of fuel in the blood. Failure to supply chemical energy in fuel abundance can cause chronic fatigue syndrome which is an important problem and the etiology of which has not been establihed.
5. ACC and FAS enzyme expressions have been detected in brain neurons, (166) this means that the malonyl-CoA metabolism is active in the brain. The brain, the most important organ where glucose can be transported without need for insulin, incurs the toxic effects of the increased malonyl-CoA concentration in fuel abundance resulting from DRCPF and stays in a chronic hyperstimulated state. This might be setting the stage for the neuropsychiatric disorders increasing enormously in developed countries.
6. Heart muscle works continuously and shows contraction differences in changing conditions. Especially failing to perform fatty acid oxidation adequately which is the basic fuel of the post-absorbtive period in DRCPF engenders metabolic ischemia years before atherosclerotic mechanical plugging ischemia. Moreover, rhythm disorders can ensue as a result of the ion and signaling alterations caused by fatty acid metabolites inside the cell. In the long term, the outcome can be heart failure as a result of cardiomyocyte loss originating from lipotoxic apoptosis.
7. Atherosclerosis and the complications related to it will be inevitable in the abundance of predisposing factors such as atherogenic dislipidemia, hyper-insulinemia, protein acylation and oxidative metabolite accumulation resulting from DRCPF.
8. A neoplastic process might be started in susceptible cells as a result of DRCPF which leads to the overproduction of some proteins (overexpression) with the compulsive effects of glucose and non-oxidized fatty acid metabolite on the genetic material.

Novel treatment approaches

1. Rearrangement of the diet composition

a) Withdrawing refined carbohydrates from the diet which form the basis of modern nutrition and are high in glycemic index (167, 168).

b) Instead of these, heading towards carbohydrate sources processed to a lesser extent and rich in fibers having a low glycemic index.

c) Offsetting the daily energy gap originating from diminished carbohydrates by means of novel balanced increases in proteins and fats (169).

d) Mixed fats and adequate cholesterol amounts should be provided in order not to increase the production of endogenous saturated fatty acids and uncontrolled cholesterol synthesis resulting from the impairment of biologic biofeedback functioning between fat and cholesterol intake with the diet and endogenous fat and cholesterol synthesis.

2. In people not performing exercise for a long time, heavy exercise increases glycogenolysis leading to the prevention of fatty acid oxidation

mediated by glucose and malonyl-CoA (170, 171). Hence, through organizing mild exercise programs, the favorable effects of enhanced fatty acid oxidation on obesity and the other parameters of metabolic syndrome must be utilized.

3. I believe that providing control of the ACC enzyme activity responsible for malonyl-CoA synthesis will constitute an important choice of treatment for metabolic syndrome. In animal studies, the perfusion of 5-aminoimidazole-4-carboxamide 1β-D-ribofuranoside (AICAR) causes ACC phosforylation (ACC inhibition) with the activation of AMPK (172). This leads to reduced malonyl-CoA and consequently to increased fatty acid oxidation (173, 174). To state it more clearly, administering AICAR will increase fatty acid oxidation as if a resting muscle was doing mild exercise (174). Therefore, using this synthetic AMPK activator, or the pharmacologic development of natural ACC inhibitors found in the daily nutritional foods people consume would provide a novel, potent and metabolically effective method for the treatment of obesity and metabolic syndrome.

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