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Beyond Dietary Fatty Acids as Energy Source: A Point of View for the Prevention and Management of Type 2 Diabetes

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1. Introduction

Dietary fatty acids have been traditionally viewed as substrates for the generation of high-energy molecules and as precursors for the biosynthesis of macromolecules. However, accumulating data from multiple lines of evidence suggest that dietary fatty acids are linked to the pathogenesis of type 2 diabetes, which involves abnormalities in both insulin secretion and action (Lopez et al., 2010).

Dietary fatty acids are absorbed into epithelial cells of the small intestine, are assembled into nascent triglyceride-rich lipoproteins, enter the bloodstream, and are transported to peripheral tissues. Therefore, the main physiological — but sometimes pathological — contribution to plasma triglycerides and tissue fatty acids, in terms of both quantity and quality, occurs during the postprandial period (Miles & Nelson, 2007). Acute elevation in plasma triglycerides, which may produce local elevation of fatty acids in beta-cells, is related to the increase of glucose-induced insulin secretion (Lopez et al., 2008; Lopez et al., 2010). Adipose tissue serves as a triglyceride storage site and, when necessary, stored triglycerides in adipocytes can be hydrolyzed by their adipose triglyceride and hormone-sensitive lipases to release fatty acids into the bloodstream. Excessive rates of lipid turnover have been shown to precede the development of type 2 diabetes in subjects with a family history of type 2 diabetes and nondiabetic obese individuals (Cusi, 2009). Decreased insulin sensitivity in adipose tissue is characterized by the increase of lipolysis and plasma fatty acid levels despite hyperinsulinemia, and impaired suppression of plasma fatty acid levels by insulin. This elevation in the plasma fatty acids, if chronic, induces a decrease in hepatic and skeletal muscle insulin sensitivity and detrimental effects on beta-cell function, which has been referred to as lipotoxicity (Giacca et al., 2011). Here, we review studies in insulin-secreting cell lines, islet cells, animal models, and human beings that have informed our current understanding of the mechanistic links among dietary fatty acids, beta-cell function, and insulin sensitivity.

2. Types of major dietary fatty acids

A fatty acid is a carboxylic acid that often has a long unbranched aliphatic chain. Fatty acids are divided into SFA and unsaturated fatty acids based on structural and chemical

properties (Fig. 1). SFA do not contain any double bonds or other functional groups along the chain, which is fully saturated with hydrogen atoms. Palmitic acid (16:0) is composed of 16 carbon atoms and is the principal SFA in the diet. SFA is found chiefly in animal products, including meats and dairy foods, but is also found in some plant sources, including coconut, cottonseed, and palm kernel oils. MUFA are unsaturated fatty acids that contain one pair of carbon atoms linked by a cis double bond. The major dietary MUFA is oleic acid (18:1n-9), which has 18 carbon atoms with the double bond occurring 9 carbon atoms away from the methyl end of the fatty acid molecule. Oleic acid is the primary component of olive oil, but also can be found in hazelnut, canola, and peanut oils. A carbon chain that contains two or more cis double bonds with the first double bond located between the third and fourth or sixth and seventh carbon atom from the methyl end of the fatty acid molecule characterises the families of n-3 or n-6 PUFA. These families cannot be

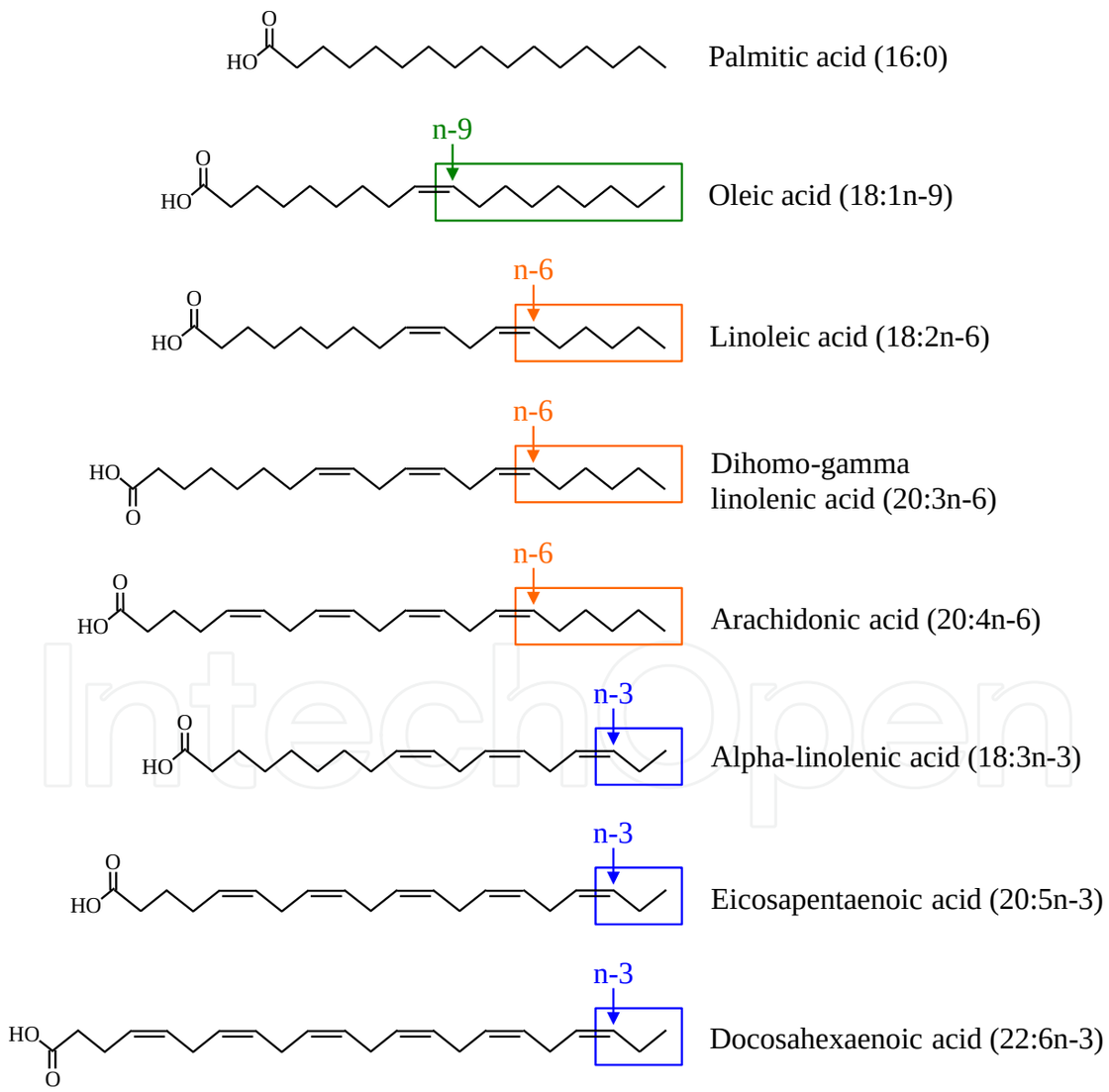

Fig. 1. The structure of the most significant dietary fatty acids.

synthesised by the human body (double bonds can be introduced into all positions of the fatty acid chain except for the n-3 and n-6 positions) and must be obtained from the diet either as alpha-linolenic acid (18:3n-3) and linoleic acid (18:2n-6), or their long-chain PUFA derivatives (Das, 2006). Of these fatty acids, eicosapentaenoic acid (20:5n-3), docosahexaenoic acid (22:6n-3), dihomo-gamma linolenic acid (20:3n-6), and arachidonic acid (20:4n-6) are the most metabolically significant. While conversion of linoleic acid to dihomo-gamma linolenic acid and arachidonic acid is typically very efficient, conversion of alpha-linolenic acid to eicosapentaenoic acid and docosahexaenoic acid is much less so (Brenna et al., 2009). This fact has particular importance in people with compromised alpha-linolenic acid availability or conversion enzyme activity. Therefore, not only alpha-linolenic acid and linoleic acid but also long-chain n-3 PUFA should be considered as essential fatty acids. Linoleic acid and alpha-linolenic acid can be found in vegetable oils, linoleic acid in safflower, sunflower, soybean, maize, and cottonseed oils, and alpha-linolenic acid in flaxseed, blackcurrant, walnut, rapeseed, and soybean oils. Eicosapentaenoic acid and docosahexaenoic acid are abundant in cold-water fatty fish, including herring, sardines, mackerel, salmon, tuna, and shellfish.

Requirements in MUFA, n-3 and n-6 PUFA are satisfied by the diet. MUFA can be synthesised from acetyl-CoA within mammalian tissues. However, it is unclear whether the entire MUFA requirement can be met by de novo metabolic machinery. MUFA, and specifically oleic acid, represent one of the core components of the Mediterranean diet (mainly due to the liberal use of virgin olive oil), which represents a prototypical dietary model associated with a long life expectancy and a low occurrence of chronic diseases, including type 2 diabetes (Lopez-Miranda et al., 2010).

3. Dietary fatty acids on insulin secretion

3.1 Acute and long-term in vitro or animal studies

Pancreatic beta-cells can respond to dietary fatty acids at the metabolic, signal transduction and transcriptional levels to promote or attenuate beta-cell function or survival (Torres et al., 2009). The ability of fatty acids to acutely induce insulin secretion spans a remarkably broad range, increasing and decreasing with chain length and degree of unsaturation, respectively. Oleic acid elicits half the insulinotropic potency of palmitic acid in perfused rat pancreas. Furthermore, acute exposure of rat insulinoma INS-1 cells to oleic acid enhances insulin production and even reverses the inhibitory effect of TNF-alpha (Vassiliou et al., 2009). This output of insulin from beta-cells can be mediated by different metabolic processes, which are activated once the fatty acids reach the cytoplasm and/or bind to cell surface platforms, including G protein-coupled receptor 40 (GPR40) (Morgan & Dhayal, 2009) and fatty acid translocase FAT/CD36 (Wallin et al., 2010). On the contrary, long-term (chronic) exposure of human islet cells to palmitic acid impairs glucose-stimulated insulin secretion, reduces insulin gene transcription and induces beta-cell apoptosis (lipotoxicity) (Giacca et al., 2011), whereas oleic acid is cytoprotective for beta-cells and even attenuates the proapoptotic effects of palmitic acid (Morgan, 2009). There are a growing number of proposed mechanisms regarding the toxicity of palmitic acid in beta-cells, ranging from physical and chemical rearrangement of lipid stores to transcriptional regulation of lipogenic genes (Poitout et al., 2009). Endoplasmic reticulum (ER) homeostasis is particularly affected by a sustained hypersecretory activity of beta-cells to fatty acids (Cnop et al., 2010). Other effects include direct ER Ca^{2+} depletion, an increase in phosphorylation of the ER Ca^{2+} sensor

protein kinase R-like ER kinase (PERK), and an increase in the protein level of transcription factor C/EBP-homologous protein (CHOP) (Gwiazda et al., 2009). Palmitic acid-induced INS-1 beta-cell death involves the activation of the stress-related C-Jun N-terminal kinase (JNK) pathway through Toll-like receptor 4 (TLR4) (Lee et al., 2011). It is notable that the precise mechanisms by which oleic acid antagonizes the deleterious effects of palmitic acid in beta-cells remain unknown.

In a mouse model of haploinsufficiency of beta-specific glucokinase ($Gck^{+/-}$), where animals have a normal beta-cell mass but impair insulin secretion in response to glucose, dietary linoleic acid was recently found to exacerbate beta-cell ER stress and apoptosis (Shirakawa et al., 2011). An increase in CHOP-positive nuclei and terminal deoxynucleotidyltransferase-mediated dUTP-biotin nick-end labelling (TUNEL)-positive apoptotic nuclei were observed in pancreatic beta-cells of $Gck^{+/-}$ mice fed a diet rich in sucrose and linoleic acid, when compared with a diet rich in sucrose and oleic acid. These effects were not evident in euglycemic wild-type or insulin receptor substrate-1 deficient (IRS-$I^{-/-}$) mice, indicating that hyperglycemia amplifies fatty acid-induced beta-cell ER stress and lipotoxicity. Likewise, the expression levels of CHOP, activating transcription factor 4 (ATF-4), and cleaved caspase-3, and the Bax/Bcl-2 ratio significantly increase in pancreatic islets from wild-type mice or stably transformed insulinoma cell line MIN6 when exposed to linoleic acid or palmitic acid in comparison with oleic acid in the presence of high-glucose concentration.

3.2 Human postprandial studies: saturated fatty acids versus monounsaturated fatty acids

Exaggerated postprandial hypertriglyceridemia is an inherent feature of diabetic dyslipidemia and is frequently found even in diabetic patients with normal fasting triglycerides (Tentolouris et al., 2008). Such phenomena would be consistent with studies linking SFA-rich meals to dysfunctions in insulin secretion and the frequency of type 2 diabetes (Misra et al., 2010). It is probable that MUFA, PUFA, and SFA could compete at the level of the beta-cell (Fig. 2). The islet tissue, which expresses LPL, could access triglycerides from postprandial triglyceride-rich lipoproteins (TRL) as a source of free fatty acids, in which case, the type and concentration of the fatty acid in the immediate vicinity of the beta-cells is likely to be dependent on the nature of the dietary fatty acids (Lopez et al., 2010). As indicated above, the input of fatty acids into the beta-cell can be mediated by cell surface platforms (GPR40 and FAT/CD36), but apoE-dependent and independent recognition sites could also cooperate with LPL to selectively remove postprandial TRL and to immediately generate intracellular fatty acids via catabolic pathways (Lass et al., 2011; von Eckardstein & Sibler, 2011).

When compared to SFA (i.e., palmitic acid)-rich meals, MUFA (i.e., oleic acid)-rich meals induce a lower early postprandial insulin response in healthy subjects (Lopez et al., 2008). These findings are consistent with the notion that in comparison with palmitic acid, oleic acid might moderate the compensatory hyperactivity of beta-cells in the postprandial state, although whether this maintenance of glucose tolerance during feeding periods could prevent or delay the development of overt type 2 diabetes remains to be elucidated.

Fasting hypertriglyceridemia results from either overproduction of triglycerides by the liver, impaired lipolysis, or a combination of both. In hypertriglyceridemic patients, the overproduction of triglycerides is disproportionately greater than the increase in apoB100 production, resulting in the formation of large triglyceride-rich VLDL particles (Caslake &

Packard, 2004). Obesity and insulin resistance result in increased hepatic supply of fatty acids and overproduction of triglycerides. Insulin inhibits VLDL production in an effort to reduce the postprandial triglyceride response to a high-fat meal. A recent randomised and within-subject crossover study in volunteers who were newly diagnosed with type IIb or IV hyperlipoproteinemia revealed that postprandial beta-cell function is buffered with MUFA when compared to SFA (Lopez et al., 2011), therefore extending the relationship between MUFA-rich meals and the benefits on postprandial glucose homeostasis observed in subjects with normal fasting triglyceride levels (Lopez et al., 2008) to a population of subjects with high fasting triglyceride levels.

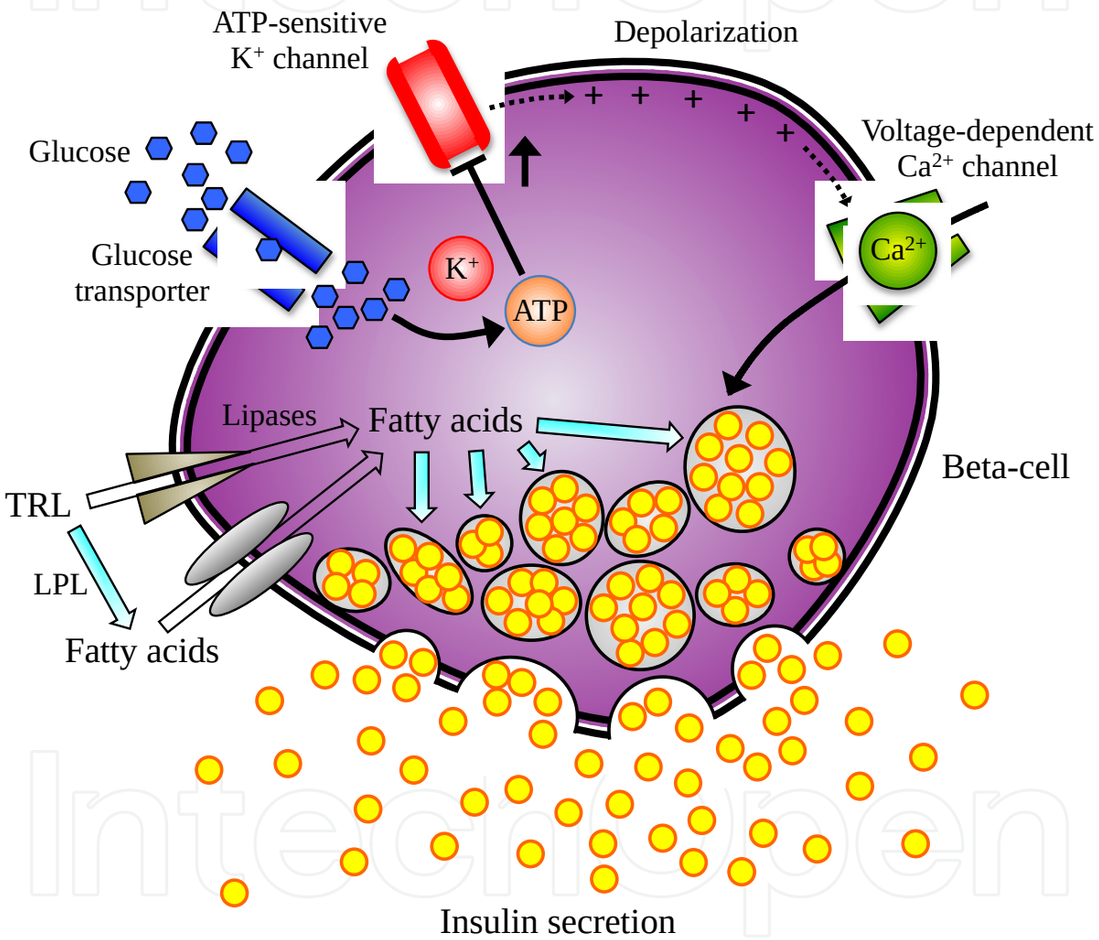

Fig. 2. The potential impact of dietary fatty acids on beta-cell function in the postprandial state.

4. Dietary fatty acids on insulin sensitivity

4.1 Long and short-term human controlled studies

Long-term habitual dietary fatty acids also relates to insulin sensitivity. However, food-frequency questionnaires do not provide reliable estimates of absolute amounts of dietary fatty acids, which may in part explain the inconsistency of long-term studies linking dietary

fatty acids with beneficial or detrimental effects on glucose metabolism. There is only consensus that a fatty acid pattern associated with decreased insulin sensitivity is characterized by high consumption of palmitic acid. The diversity of dietary fatty acids is reflected in plasma lipids and tissues. For example, the fatty acid composition in adipose tissue partially reflects the consumption of dietary fatty acids over a considerable time, but also reflects the activities of enzymes responsible for fatty acid synthesis, desaturation, and elongation. In a recent observational study, palmitic acid in adipose tissue was negatively linked to insulin sensitivity in a large community-based cohort of elderly men (Iggman et al., 2010). It was also found a positive association between oleic acid, linoleic acid, and alpha-linolenic acid in adipose tissue and insulin sensitivity. Furthermore, decreased insulin sensitivity and type 2 diabetes are related to increased pancreatic cancer risk. A positive association of palmitic acid intake, mainly from red meat and dairy products, with pancreatic cancer has been recently described in men and women after a mean of 6.3 years of follow up (Thiebaut et al., 2009).

Despite the reasonable replacement for SFA in terms of risk factor for chronic diseases in general and type 2 diabetes in particular are MUFA, because the consumption of n-3 and n-6 PUFA is limited to less than 10% of the total daily calories, most studies have involved n-3 and n-6 PUFA for investigating the association between long and short-term dietary fatty acid consumption and insulin sensitivity. There is no clear evidence to suggest that n-3 PUFA improve insulin sensitivity in humans. Very high doses of n-3 PUFA may even impair insulin sensitivity in subjects with type 2 diabetes (Mostad et al., 2006). However, after only 5 weeks, the insulin sensitivity is improved in volunteers (healthy, obese, and type 2 diabetics) when SFA are replaced by n-6 PUFA (Summers et al., 2002). Similar findings are observed in overweight individuals after substitution of SFA with MUFA (Lovejoy et al., 2002).

The mechanisms by which dietary fatty acids influence insulin sensitivity have been previously reviewed (Riserus, 2008). The fatty acid composition of cell membrane may be affected by dietary fatty acids, and then cell membrane functions, e.g., translocation of glucose transporters, membrane fluidity, ion permeability, and/or insulin receptor binding/affinity. Dietary fatty acids can also improve hepatic insulin sensitivity by suppressing lipogenic gene expression and hepatic lipogenesis, and stimulating hepatic fatty acid oxidation. SFA, palmitic acid in particular, have a contrary effect. Different observational studies suggest that the level of palmitic acid intake may even independently predict type 2 diabetes (Hodge et al., 2007).

4.2 Human postprandial studies: saturated fatty acids versus monounsaturated fatty acids

Dietary fatty acid quality, rather than quantity, has been suggested to acutely influence insulin sensitivity in humans (Lopez et al., 2010). Compensatory hyperinsulinemia due to enhanced beta-cell function is considered to be an obligate accompanying feature in insulin resistance syndromes (Reaven, 2005). Euglycemic clamps or frequently sampled intravenous glucose tolerance tests are the reference methods to determine beta-cell sensitivity to glucose and the sensitivity of body tissues to insulin (Cobelli et al., 2007). However, these tests are far from physiological because insulin secretion or activity is only measured in the steady-state. Empirical and model-based indices based on the oral glucose tolerance test (OGTT) provide a reasonable approximation of postprandial beta-cell function and whole-body

insulin sensitivity (Bartoli et al., 2011). An important caveat of the OGTT is that the events associated with the ingestion of a pure glucose solution are not wholly equivalent to the numerous metabolic events associated with eating a mixed high-fat meal when both carbohydrates and fatty acids are ingested.

It has been hypothesised that insulin resistance syndromes might be a postprandial phenomenon linked to the acute metabolism of dietary fatty acids (Pedrini et al., 2006). When mixed high-fat meals with different proportions of dietary fatty acids are administered to healthy subjects, they become less insulin resistant postprandially as the proportion of MUFA to SFA, and oleic acid to palmitic acid, in dietary fatty acids increase (Lopez et al., 2008). In subjects who were newly diagnosed with type IIb or IV hyperlipoproteinemia, postprandial insulin sensitivity is also improved with MUFA when compared to SFA (Lopez et al., 2011). Furthermore, with regard to resistance to insulin-mediated glucose disposal, SFA (i.e., palmitic acid) was found to stimulate additional insulin secretion to maintain postprandial glucose homeostasis, suggesting a mechanism of lipid-induced deterioration of insulin sensitivity coupled with compensatory insulin secretion that is distinctively modulated by dietary fatty acids.

5. Conclusion

Dietary fatty acids are nutrient signals that play a relevant role in modulating insulin secretion and action. SFA, particularly palmitic acid, are associated with damage of glucose-stimulated insulin secretion and lipotoxicity in beta-cells and with decline of insulin sensitivity. MUFA, particularly oleic acid, are cytoprotective for beta-cells, even attenuate the cytotoxic effects of palmitic acid, and improve insulin sensitivity in comparison with SFA. PUFA, either of n-3 or n-6 family, do not confer additional benefit over MUFA. Therefore, efforts to promote the consumption of MUFA in place of SFA should be relevant as part of a dietary lifestyle strategy to prevent or manage type 2 diabetes.

6. Acknowledgment

The work was supported by MICINN grants AGL2004-04958, AGL2005-03722, and AGL2008-02811, CSIC grants to L.M.V. and B.B., MICINN grants to A.O., and Marie Curie grant PERG07-GA-2010-268413. L.M.V., A.O, S.L., and B.B. are considered equal first authors.

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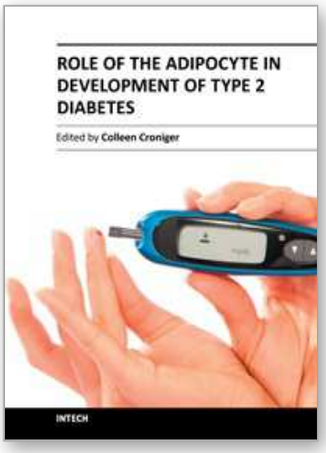

Role of the Adipocyte in Development of Type 2 Diabetes

Edited by Dr. Colleen Croniger

ISBN 978-953-307-598-3
Hard cover, 372 pages
Publisher InTech
Published online 22, September, 2011
Published in print edition September, 2011

Adipocytes are important in the body for maintaining proper energy balance by storing excess energy as triglycerides. However, efforts of the last decade have identified several molecules that are secreted from adipocytes, such as leptin, which are involved in signaling between tissues and organs. These adipokines are important in overall regulation of energy metabolism and can regulate body composition as well as glucose homeostasis. Excess lipid storage in tissues other than adipose can result in development of diabetes and nonalcoholic fatty liver disease (NAFLD). In this book we review the role of adipocytes in development of insulin resistance, type 2 diabetes and NAFLD. Because type 2 diabetes has been suggested to be a disease of inflammation we included several chapters on the mechanism of inflammation modulating organ injury. Finally, we conclude with a review on exercise and nutrient regulation for the treatment of type 2 diabetes and its co-morbidities.

How to reference

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Lourdes M. Varela, Almudena Ortega, Sergio Lopez, Beatriz Bermudez, Rocio Abia and Francisco J.G. Muriana (2011). Beyond Dietary Fatty Acids as Energy Source: A Point of View for the Prevention and Management of Type 2 Diabetes, Role of the Adipocyte in Development of Type 2 Diabetes, Dr. Colleen Croniger (Ed.), ISBN: 978-953-307-598-3, InTech, Available from: http://www.intechopen.com/books/role-of-the-adipocyte-in-development-of-type-2-diabetes/beyond-dietary-fatty-acids-as-energy-source-a-point-of-view-for-the-prevention-and-management-of-typ

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