Wydawnictwo UR 2023
ISSN 2544-1361 (online)
doi: 10.15584/ejcem.2023.2.19

http://www.ejcem.ur.edu.pl
European Journal of Clinical and Experimental Medicine
Eur J Clin Exp Med 2023; 21 (2): 357–364

REVIEW PAPER

Relationship between obesity, insulin resistance and cell membrane properties

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ABSTRACT

Introduction and aim. The obesity is one of the greatest public health problems in developing countries and it is a triggering factor for diabetes associated with insulin resistance. The importance of cell membrane lipids as essential regulators of insulin resistance, since changes in the dynamic properties of the cell membrane (e.g., membrane fluidity), could be one of the events by which obesity affects insulin sensitivity. Thus, the insulin resistance may not only be a cause but also a consequence of lipid disorders such as dyslipidemia and/or cell membrane phospholipid composition change. The modification of plasma membrane lipid composition can change membrane biophysical properties and thus influencing protein-lipid interactions, enzymatic activity and regulation of surface receptors. Alterations in the lipid composition modify the fluidity of plasma membranes and the expression of membrane functions, such as receptor binding and enzyme activities. This review summarizes the current knowledge on the effects of the modulation of plasma membrane lipid composition and membrane fluidity in the functionality of membrane proteins involved in insulin activity, including the insulin receptor, glucose transport and Na^+/K^+ ATPase and, in turn, the key features of the metabolic syndrome.

Material and methods. References for that article were found through PubMed and Google Scholar, using terms: "obesity", "insulin resistance" and "membrane properties". The research was limited to abstracts and available full-text articles.

Analysis of the literature. There is a strong relationship between dietary lipids, membrane lipid profiles and insulin resistance. The changes in the dynamic properties of the cell membrane (e.g., membrane fluidity), could be one of the events by which obesity affects insulin sensitivity. The modification of plasma membrane lipid composition can change membrane biophysical properties and thus influencing protein–lipid interactions, enzymatic activity, and regulation of surface receptors. Modifications of membrane phospholipid composition could have a role in the insulin action by altering membrane fluidity and, as a consequence, the insulin signaling pathway.

Conclusion. As conclusion the membrane-lipid therapy approach can be used to treat important pathologies such as obesity and many others diseases such as : cancer, cardiovascular pathologies, neurodegenerative processes, obesity, metabolic disorders, inflammation, and infectious and autoimmune diseases. This pharmacological strategy aims to regulate cell functions by influencing lipid organization and membrane fluidity, inducing a concomitant modulation of membrane protein localization and activity which might serve to reverse the pathological state. Through this review we suggest an in-depth analysis of the membrane lipid therapy field, especially its molecular bases and its relevance to the development of innovative therapeutic approaches.

Keywords. insulin resistance, membrane properties, obesity

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Received: 1.02.2023 / Revised: 24.03.2023 / Accepted: 28.03.2023 / Published: 30.06.2023

Ahyayauch H. *Relationship between obesity, insulin resistance and cell membrane properties.* Eur J Clin Exp Med. 2023;21(2):357–364. doi: 10.15584/ejcem.2023.2.19.

Introduction

The metabolic syndrome (MetS) is becoming a matter of great concern throughout the world. MetS is a group of risk factors than can lead to heart disease and type 2 diabetes (T2DM): insulin resistance, high blood pressure and obesity. The overall prevalence of the metabolic syndrome in the USA is 33–39%, with significantly higher prevalence in women compared with men.[1,2] In European countries, the MetS has an estimated prevalence below 18% in Denmark or in Spain the prevalence is above 30%.[2,3] Obesity is a major risk cause of several comorbidities such as cardiovascular diseases, type II diabetes, cancers and other health problems.[4]

Overweight and obesity are significant risk factors for developing the MetS and are the major nutrition-related disorders worldwide. The prevalence of obesity is one of the greatest public health problems also in developing countries that have undergone important changes in lifestyle, eating habits and physical activity in the last years.[5] More than 1 billion people worldwide are obese, 650 million adults, 340 million adolescents and 39 million children. This number is still increasing. WHO estimates that by 2025, approximately 167 million people adults and children will become less healthy because they are overweight or obese. WHO estimates that 59% of adults are living with overweight or obesity, with more than half of adults in 50 out of 53 Member States in the European Region living with overweight or obesity. Levels are higher among males (63%) than among females (54%) across the WHO European Region and in most countries. Obesity occurs when dietary energy intake exceeds energy expenditure. Extrapolations of the literature findings to alterations of membrane function, relevant to the pathogenesis of obesity, are speculative, although attractive. Altered lipoprotein and phospholipid metabolism could be responsible for the perturbation of plasma membrane composition and physical properties; these would, in turn, affect the structural

and functional properties of membrane enzymes and yield, as a consequence, impaired ion transport and abnormal thermogenesis, which may be involved in the pathogenesis of obesity.

However, it should be mentioned that diet intervention is also a powerful tool to prevent the development of the obesity, healthy diets and particularly dietary fatty acids have been shown to have a protective role against the metabolic syndrome. Particularly, dietary fatty acids, among other mechanisms, by modifications of the lipid composition of the membranes in insulin-sensitive tissues.

Aim

The architectural influence of the plasma membrane on insulin action, particularly the molecular events regulating insulin receptor binding and glucose transport, is the focus of this review.

Material and methods

References for that article were found through PubMed and Google Scholar, using terms: "obesity", "insulin resistance" and "membrane properties". The research was limited to abstracts and available full-text articles.

Analysis of the literature

Dietary lipid and insulin resistance

Healthy diets rich in fruits, vegetables, grains, fish and low-fat dairy products have a protective role.[6] The quality of dietary fat is also determinant in the effect of diet on insulin sensitivity and the metabolic syndrome. Diets high in saturated fatty acids (SFA) impair both insulin sensitivity and blood lipids, while substituting carbohydrates or monounsaturated fatty acids (MUFA) for SFA revert these abnormalities in both healthy and diabetic subjects.[7-10]

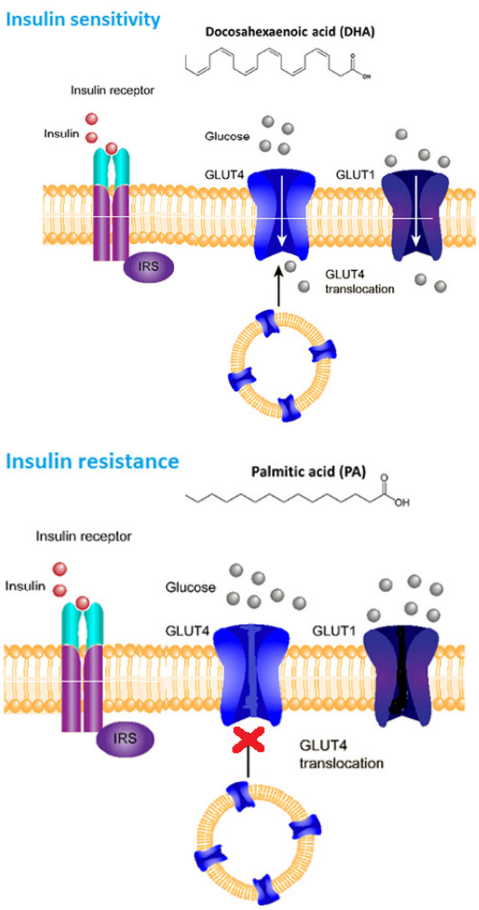

Fig. 1. Schematic diagram showing the role of dietary fatty acid on insulin signaling pathway

Cell membrane phospholipid composition is regulated by the fatty acid composition of dietary fat, being especially sensitive to n-6 and n-3 polyunsaturated fatty acids (PUFA), with a preference for the latter.[11,12] In contrast, membrane SFA and MUFA content is not as

dependent on the dietary fatty acid profile, as these fatty acids can be synthesized endogenously. Many studies have demonstrated a strong relationship between dietary lipids, membrane lipid profiles and insulin resistance, with high SFA diets leading to insulin resistance, whereas diets high in n-3, with a low n-6/ n-3 ratio, keeping insulin action at normal levels.[12-14] Many reports have shown that a high intake of dietary SFA significantly worsens insulin resistance, in particular through modifications in the composition of cell membrane phospholipids. Palmitic acid has been shown to have the capability to induce insulin resistance in the liver.[13] For instance, palmitic acid exposure resulted in the accumulation of ceramides and diacylglycerol, developing insulin resistance, reduction of hepatic GLUT-2 expression and decreased glucose uptake (Fig 1).

However studies of oleic acid have reported contradictory results. Some studies have shown an increase in insulin sensitivity with diets rich in oleic acid, whereas others have shown an inverse association between oleic acid and insulin sensitivity.[13,14]

The type and amount of dietary lipids influence the lipid composition of cell membranes and modulate the interactions with proteins involved in the regulation of insulin sensitivity but also processes associated with other components of the metabolic syndrome like dyslipidemia and hypertension. The effects, at least in part, are probably mediated by modification of the composition and structural properties of plasma membranes.[15]

Membrane properties and obesity

Membrane lipid composition and obesity

Changes in erythrocyte membrane phospholipid composition, especially in obese subjects, parallel those in membrane of other tissues providing a helpful model to study the effects of insulin resistance in plasma membrane.[16] The alterations in lipid composition and fluidity exist in erythrocytes from obese subjects.

Many studies have shown that erythrocyte membrane fatty acid composition in obese adolescents differs from that in age and sex matched lean controls, reflecting a decrease in n-3 PUFA and MUFA and an increase in SFA, especially in very-long chain SFA, like 24:0.[17] In addition, the erythrocyte membranes from obese subjects are characterized by a higher cholesterol/phospholipid ratio, which has been used as an index of membrane fluidity.[15] Membranes enriched in cholesterol and SFA and decreased in MUFA and PUFA showed enhancement of membrane rigidity, affecting the signaling pathways related to membrane proteins. It has also been proposed that insulin resistance may not only be a cause but also a consequence of lipid disorders such as dyslipidemia and/or cell membrane phospholipid composition abnormalities.

Min et al. described a decrease in the phospholipid phosphatidylethanolamine and arachidonic (20:4, AA) and docosahexaenoic (22:6, DHA) acids in red blood cells (RBC) from patients with gestational diabetes, often linked to obesity.[18] Other work of Cazzola et al. reported on an increase in the cholesterol/phospholipid ratio in RBC membranes from obese patients, together with a decrease in ω-3 fatty acids (e.g., DHA) and an increase in ω-6 (e.g., AA).[19] In the same way Pietiläinen et al. found increased proportions of palmitoleic acid (16:1) and AA, together with increased levels of ethanolamine plasmalogens in adipose tissue of the obese twins.[20] Recently, studies from Arranz group have found that, in children with obesity RBC membranes, saturated and trans-unsaturated fatty acyl chains were increased.[21] In a parallel study, they found that monounsaturated chains were decreased in obese children.[22]

The modification of plasma membrane lipid composition can change membrane biophysical properties and thus influencing protein-lipid interactions, enzymatic activity, and regulation of surface receptors.[23-25] Modifications of membrane phospholipid composition could have a role in the insulin action by altering membrane fluidity and, as a consequence, the insulin signaling pathway.

Membrane fluidity and obesity

Numerous studies have shown that changes in the dynamic properties of the cell membrane (e.g., membrane fluidity), could be one of the events by which obesity affects insulin sensitivity.[26] The particularity of this review is that we have focused on the nature of the phospholipids and sphingolipids presents in the membrane cell of the obese people and which may be the cause of this disease. Alterations in the lipid composition, particularly the relative proportions of cholesterol and phospholipids, modify the fluidity of plasma membranes and the expression of membrane functions, such as receptor binding and enzyme activities.[27] Many studies have demonstrated that some kind of lipids play a crucial role in the insulin-resistance. The insulin-resistant state was positively correlated with membrane sphingomyelin, phosphatidylethanolamine, and phosphatidylcholine contents, and negatively with phosphatidylinositol contents in the whole population. Multivariate regression analyses showed that two membrane parameters, phosphatidylethanolamine and sphingomyelin, were among the independent predictors of insulin resistance in the whole population, but also in the lean and the obese groups separately.[16] Intervention induced a significant reduction in body weight, fat mass, and insulin resistance. More important, the reduction in insulin resistance was directly associated with reduction in sphingomyelin and phosphatidylethanolamine contents. These results suggest that the abnormalities in the membrane phospholipid composition could be included

in the unfavorable lipid constellation of obesity, which correlated with impaired insulin sensitivity.

Measurement of membrane fluidity by steady-state fluorescence polarization is the most common technique to assess the physical state of the cell membrane.[28] The fluorescence anisotropy of a membrane probe is an inverse of the fluidity of the lipid region where it is situated. Various cellular functions that may be involved in insulin action, such as enzyme activity, ion and substrate transport, and receptor binding and capping, are modulated by the physical properties of the cell membrane. Beguinot and his collaborators demonstrated that erythrocyte membrane phospholipid composition is related to hyperinsulinemia in obese nondiabetic women.[29] This study shows that both the membrane cholesterol/phospholipids ratio and the fluorescence polarization of DPH in erythrocytes obtained from obese subjects were significantly higher than in erythrocytes from healthy subjects. The higher cholesterol/phospholipids ratio was generated by a net increase in cholesterol and a net decrease in total lipid-bound phosphorus; it was not associated with altered plasma concentrations of total cholesterol and triglycerides. The increased C/P ratio in erythrocytes is due to an average 2-fold increase in cholesterol with normal or elevated phospholipid levels compared to a 20% decrease in membrane phospholipids and a 17% increase in cholesterol in the erythrocytes from obese subjects.[30-31] More recently, surprising results was found by Sot and his collaborators, they show a clear tendency for obese patient RBC to exhibit a higher fluidity in their membranes, or, more specifically, at the polar–non-polar interface of the membrane bilayers than the control cohort. This group try to explain these results doing Lipidomics, they found significant changes in concentration of ω-3 and ω-6 fatty acids.[32] More precisely, obese patient RBCs undergo an increase is some ω-6 fatty acids such as arachidonic acid, while reducing ω-3 ones, such as DHA. In the other part, a significant reduction in SM is detected for obese patient RBC. Both events, SM reduction and, perhaps more decisively, the increase of ω-6 fatty acids seem to contribute to the afore mentioned fluidity of obese patient RBC membranes.

Membrane properties and insulin resistance

The mechanisms by which obesity predisposes to insulin resistance remain poorly understood. However, insulin resistance could be related to changes in cell membrane properties.

Many cellular functions involved in insulin action are modulated by the physical properties of the cell membrane, such as enzyme activity, ion and substrate transport, and receptor binding.[33] Consequences of structural alterations of plasma membrane properties include reduced Na^+-K^+ ATPase, decreased concentration of insulin receptors and decreased glucose transport.

Insulin secretion and insulin receptor binding

The β-cells respond to many nutrients in the blood circulation, including glucose, other monosaccharides, amino acids, and fatty acids, the amplitude of insulin secretion induced by glucose is much larger compared with that stimulated by protein or fat. The metabolism of glucose and other nutrients causes depolarization of the B-cells which subsequently causes an increase in intracellular Ca^{2+} and insulin secretion. Elevation of intracellular cAMP and activation of Ca^{2+}/phospholipid-dependent protein kinase C (PKC) have also been implicated in the regulation of insulin secretion. Glucose is also known to stimulate the generation of arachidonic acid (AA), and its metabolites, prostaglandins and hydroxyeicosatetranoic acids in pancreatic islets.[34,35] Arachidonic acid is known to release intracellular Ca^{2+} in several cell types, presumably from the endoplasmic reticulum and it is feasible that such a mechanism may underlie the effects of AA on insulin release since we have shown that elevations in cytosolic Ca^{2+} alone are sufficient to initiate insulin release.[36,37]

If AA is acting as a physiological fusogen by affecting membrane fluidity we might predict that structurally similar fatty acids would have similar effects, and the results of Band group demonstrate that eicosapentanoic acid and docosahexaenoic acid, but not eicosatrienoic acid, stimulate insulin release.[38] In contrast, oleic and linoleic acid are also produced in glucose stimulated islets and possess some fusogenic activity.[35,39] However, those fatty acids were relatively ineffective in stimulation of insulin secretion.[38]

The plasma membrane plays an important role in containing numerous proteins involved in receiving signals from hormones, growth factors, and other molecules. The first step of a metabolic cascade leading to glucose uptake is the binding of insulin to its receptor in the cell membrane. The activity of the insulin receptor, as well as its affinity to insulin depend on the fluidity of the cell membrane, which, in turn, are dependent on the membrane lipid composition. Increasing SFA content in phospholipids decrease membrane fluidity and leads to a decrease in the number of insulin receptors and the affinity of insulin to them. On contrary, increasing PUFA content in phospholipids increase membrane fluidity and improve insulin sensitivity.[40] Several studies have shown that insulin receptor signaling is impaired by low membrane fluidity, probably because lateral diffusion and localization to membrane microdomains is important for ligand binding and signaling. [41-43]

To demonstrate the relation between membrane fluidity and insulin sensitivity, the study of Tong and his collaborators was carried out with fifteen patients T2DM (ten male) and Twenty-one healthy white subjects (ten male) with normal glucose tolerance and no family history of diabetes mellitus.[44] The results shown

that the binding of insulin coincides with the conformational change and aggregation of insulin receptors.[45] The higher fluidity at the core of the diabetic leucocyte membranes may hinder conformational changes and aggregation of insulin receptors, resulting in impaired action of insulin. Interestingly, some data suggest that the antidiabetic drug metformin, by increasing membrane fluidity, may correct a protein configuration or configurations disturbed by the diabetic state.[26]

Na^+-K^+ ATPase

Sodium/potassium-ATPase is a membrane protein responsible for the active transport of Na^+ and K^+ ions across the plasma membranes of eukaryotes.[46,47] A reduction in Na^+/K^+-ATPase levels is associated with obesity and in several experimental systems, Na^+/K^+ ATPase is altered in response to changes in membrane lipid composition.[48-50] It could be speculated that membrane physical properties play a major role in maintaining ionic gradients across the bilayer, a process that involves a large amount of cellular energy.[51] In the same way, Iannello and his collaborators have shown that obesity may repress Na^+/K^+-ATPase enzyme activity, probably through the mediation of free fatty acids (FFAs), which are elevated in such cases.[52-54] FFAs, present in the membrane or as the products of phospholipase A2 (PLA2)-dependent regulatory pathway, tend to inhibit Na^+/K^+-ATPase.[55-46] Interestingly, Iannello et al. reported that Na^+/K^+-ATPase activity is reduced in the adipose tissue of obese hyperinsulinemic subjects.[52]

Glucose transport

GLUT are integral membrane proteins that contain 12 membrane spanning helices with both the amino and carboxyl termini exposed on the cytoplasmic side of the membrane. Specific transporter proteins (glucose transporters, GLUT) are required to facilitate glucose diffusion into cells according to a model of alternate conformation. GLUT4 is an insulin-regulated glucose transporter that is responsible for insulin-regulated glucose uptake into fat and muscle cells. In the basal state, GLUT4 cycles continuously between the plasma membrane and one or more intracellular compartments.[56] GLUT4 differs from other glucose transporters in that about 90% is sequestered in intracellular vesicles in the absence of insulin. Once the insulin receptor has been stimulated, the intracellular stores are translocated to muscle plasma membranes. A cascade of events culminates finally in membrane fusion with GLUT4 containing vesicles. These plasma membrane localized transporters subsequently facilitate the influx of plasma glucose into the cell.[56]

The plasma membrane is intricately involved in the initial (signal reception), intermediate (lipid and protein molecule compartmentalization), and final (GLUT4 intercalation) steps of this process. Activation of the insulin receptor triggers a large increase in the rate of GLUT4 vesicle exocytosis and a smaller but important decrease in the rate of internalization by endocytosis.[57-60]

Glucose transport across the membranes could be influenced by membrane fluidity. Moderate increases in plasma membrane fluidity have been documented to increase glucose transport.[61,62] Furthermore, it has been shown that basal glucose transport is not fully active in fat cells and can be increased further by augmenting fluidity.[61] In direct support of that finding, insulin-stimulated glucose transport is decreased when fluidity diminishes.[62] The fatty acid composition of membrane phospholipids may influence glucose transport by GLUT. Garvey et al. observed that in patients with obesity, impaired glucose intolerance, T2DM and gestational diabetes impaired GLUT-4 function or translocation occurs.[63] Weijers et al. suggested that a shift from unsaturated towards SFA in phospholipid membranes counteracts the machinery responsible for GLUT4 insertion into plasma membrane, by creating a more tight packing of phospholipids and affecting glucose transport and insulin sensitivity.[57] In addition, cholesterol depletion from plasma membrane results in an increase in the basal-state plasma membrane level of GLUT4.[64] The finding that the endocytic rate of protein retrieval from the cell surface is cholesterol dependent provides an explanation for a buildup of this transporter at the plasma membrane.[64,65]

Activation of phosphatidylinositol-3 kinase (PI3K) is one of the important steps in insulin signaling downstream of IRS, as it is involved in the translocation of GLUT4 to the cell membrane in response to the insulin signal but its activity in response to insulin can be totally inhibited by fatty acids.[66] However, whether fatty acids act on PI3K directly or mediated by PKC is still unclear. On the other hand, it has been suggested that PUFA can act as ligands of peroxisome proliferator-activated receptor-gamma or modulate its expression, thus increasing GLUT4 transcription and synthesis, and improving insulin resistance.[67,68]

Conclusion

Membrane lipid composition, membrane lipid structure, and membrane lipid fluidity influence the localization of proteins in membrane microdomains via protein–lipid interactions, facilitating specific protein-protein interactions and their resulting signals. Therefore, regulating the membrane lipid composition through pharmaceutical or nutraceutical interventions can serve to normalize signals that have been altered under different pathological conditions.

Membrane lipid therapy has emerged as a novel and innovative therapeutic concept that facilitates the design/discovery of new molecules. Molecules developed using this strategy target the membrane lipid boundary of cells and/or internal organelles, where many cellular

functions occur. The development of such new drugs is aided by the identification of the factors regulating membrane lipid structures, and their roles in cell signaling and pathophysiological processes, and such information has allowed and will facilitate the design and discovery of novel molecules for the treatment of important diseases.

Declarations

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author contributions

Conceptualization, H.A.; Methodology, H.A.; Software, H.A.; Validation, H.A.; Formal Analysis, H.A.; Investigation, H.A.; Resources, H.A.; Data Curation, H.A.; Writing – Original Draft Preparation, H.A.; Writing – Review & Editing, H.A.; Visualization, H.A.; Supervision, H.A.; Project Administration, H.A.

Conflicts of interest

The author have no conflicts of interest to declare.

Data availability

Data supporting the results of this study shall, upon appropriate request, be available from the corresponding author.

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