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Type 2 Diabetes: A Status of Long-Term Heat Acclimation

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Abstract

To understand the relationship between heat production and the onset of type 2 diabetes, a brief review highlights the concept of eukaryotic cellular energy transport. Hydrogen is the energy carrier par excellence for the energy saved in our food. After absorption of food, hydrogen is being stripped from the molecular remains of the nutrients, and passed via the citric acid cycle into the first protein complex of the mitochondrial electron-transport chain. Here electrons are separated from hydrogen, and finally donated to molecular oxygen, the ultimate electron acceptor in complex IV, to form H_2O. The remaining protons (H^+) are transferred from the matrix across the mitochondrial inner membrane into the intermembrane space. These protons could re-enter the matrix through the inner mitochondrial membrane in two different ways, i.e. through the ATP synthase protein complex for driving ATP synthesis, or through the pore of uncoupling protein (UCP) 1 without using energy for any purpose. Under these conditions, the proton potential energy is released as heat. Imagine an increased re-enter of protons through UCP1 as a result of a genetic defect. Then, the cell temperature rises, and the unsaturation index (UI; a measure of unsaturation of phospholipid fatty acyl-chains) falls. A reduction in UI lowers membrane flexibility, which in turn, reduces the amount of all functional Class I glucose transporters, promotes tissue hypoxia, and thereby reduces glucose-mediated ATP production. Cells switch to fatty-acid-mediated ATP production, which will set up a vicious cycle of raising levels of essentially saturated plasma free fatty acids and lowering the level of transmembrane glucose transport. These phenomena represent a blueprint of the onset of type 2 diabetes in human individuals.

Keywords: *Basal Metabolic Rate; Heat Acclimation; Type 2 Diabetes; Uncoupling Protein; Unsaturation Index*

Abbreviations

BMR: Basal Metabolic Rate; GLUT: Glucose Transporter; UCP: Uncoupling Protein; UI: Unsaturation Index

Introduction

The first complex eukaryotic cells arose from a single chimeric event between an archaeal host cell and a bacterial endosymbiont some 1.5 to 2 billion years ago [1]. Archaea and bacteria are similar in a number of important biochemical processes, but differ in many fundamental respects, including cell membrane composition. The composition of the phospholipid bilayer in archaea is distinct when compared to bacteria, where the hydrocarbon chains of archea consist of fully saturated methyl branched isoprenoid moieties in comparison to fatty acid derived saturated and (poli)unsaturated hydrocarbon chains of bacteria. As a result, the organization of archaeal membrane lipids resulted in stiffer membranes with a higher thermal stability compared to the bacterial phospholipids [2]. For the survival of eukaryotic cells, for instance at lower temperatures, the archeal membranes must have been replaced with bacterial membranes, early on in the eukaryotic evolution. The latter consist of sn-glycerol-3-phosphate, with saturated acyl-chains at the C1-position of glycerol and (poli) unsaturated acyl-chains at the C2-position of glycerol. This dramatic makeover resulted in membranes with an increased flexibility. So the bacterial DNA transfer to the host cell must have included the genes for bacterial lipid synthesis, which gave the complex eukaryotic cells the opportunity to change the unsaturation index (UI; number of cis-double bonds per 100 fatty acyl-chains) over a broad range of temperatures.

Temperature and fatty-acyl phospholipid composition

To deeper understand the molecular processes involved in the pathophysiology of type 2 diabetes and its prediabetic phase, and to get general agreement on a new concept definition, some important studies are summarized for answering intriguing questions about the nature of type 2 diabetes.

The 'Impaired glucose transport' study results indicated that transmembrane glucose transport was the rate-controlling step in the reduced insulin-stimulated muscle glycogen synthesis in individuals with type 2 diabetes. Moreover, the time course of insulin and its concentration in the interstitial fluid were similar in both individuals with diabetes and healthy controls [3]. Study results examining the hypothesis that reduced expression of glucose transporter (GLUT) 4 is a characteristic finding in the skeletal muscles of subjects with type 2 diabetes showed a similar expression of both GLUT4-mRNA and GLUT1-mRNA in subjects with type 2 diabetes and body-weight-matched healthy controls [4]. These data may point in the direction of conformational changes of the 3D structure of GLUTs [5], which result from alterations in membrane phospholipid composition of type 2 diabetes individuals, compared to healthy controls.

The data described above lend support to the hypothesis that a change of thermogenesis might be the cause of the decreased insulin-stimulated muscle glycogen synthesis in type 2 diabetes. In this context, cell membranes are rather sensitive to temperature fluctuations, which affect their physical-chemical properties and, consequently, the functioning of embedded proteins, including glucose transporters [6].

The adaptation of an integrated bilayer system to an environmental factor such as temperature is referred to as homeoviscous adaptation. Fine examples of homeoviscous adaptation are results of several studies, which investigated the effects of temperature acclimation on the phospholipid membrane composition of aquatic organisms. Acclimation is the process in which an individual organism adjusts to a change in its environment (such as a change in temperature). These studies consistently reported that cold acclimation generates an increase in cell membrane polyunsaturation [7,8]. So to keep a flexible and effective membrane at low temperatures, aquatic organisms actualize an increased concentration of unsaturated fatty acids relative to those at warmer temperatures [9] (Table 1). Evolution by natural selection forced cold-acclimated fishes to raise their concentration of unsaturated fatty acids. Recall that the introduction of more carbon-carbon cis-double bonds into a phospholipid fatty-acyl chain leads to an appreciable reduction in the fatty acid melting point and, consequently, to a larger value for area A, the surface of the cross-section of the cylindrical part of the phospholipid molecule (the hydrocarbon region), which increases membrane flexibility (fluidity) [10]. A fine example is the insertion of one or more carbon-carbon cis-double bounds into stearic acid (C18:0, melting point (mp) 69.9°C), oleic acid (C18:1 n-9, mp 13°C); linoleic acid (C18:2 n-6, mp -5°C), and α-linolenic acid (C18:3 n-3, mp -11°C). It is important to note that the homeoviscous adaptation is a reversible process and existed as early as the beginning of the Ordovicium, approximately 500 to 400 million years ago.

	15°C	25°C	30°C
SFAs (%)	17.84	19.92	38.40
MUFAs (%)	16.10	16.10	26.60
PUFAs (%)	65.70	61.50	34.90
UI	349.9	325.9	189.9

Table 1: *Fatty acid composition (% of total fatty acids) and UIs of membrane phospholipids in fathead minnow (Pimephales promelas) muscle*[a].

[a]*: The calculations of the UI value are based on the original data listed by Fadhlaoui., et al [9]. UI: Unsaturation Index; SFA: Saturated Fatty Acid; MUFA: Mono-Unsaturated Fatty Acid; PUFA: Poly-Cis-Unsaturated Fatty Acid.*

Recently, Hanssen., *et al*. published an extensive article reporting that 10d of cold acclimation (14 - 15°C) markedly increased peripheral insulin sensitivity by on average about 43% in eight type 2 diabetes subjects [11]. Cold acclimation resulted in an enrichment of GLUT4 at sarcolemma, which facilitated the uptake of glucose. The GLUT4 translocation could not be explained by AMPK activation or improved insulin. In my view, a cold environment leads to a reduction in membrane fluidity, which is counteracted by an increase in cell membrane polyunsaturation. The latter causes an increase in UI, which in turn, rises membrane flexibility and as a consequence favors the GLUT4 translocation.

A good example of evolutionary heat acclimation lies hidden in the relationship between the mammalian body mass (M, g) and the basal metabolic rate (BMR; ml of O_2 per hour) in an allometric equation of the form: $BMR = 4.12 \times M^{0.69}$ [12]. This relationship, with an allometric coefficient of 0.69, means that the BMR grows at a slower rate than the body mass, referred to as the slow-down principle. To understand the rationale behind the slow-down principle, let us suppose, as a thought experiment, the multi-celled development of a single-celled, cube-shaped eukaryote, which grows in a Cartesian coordinate system with the same speed in all three directions. As can be easily seen, this procedure creates a sequence of cube-shaped eukaryote generations with one cell extension in each of the three dimensions per new generation. The array number denotes the number of unit-cubes on the x-axis. Thus the first single-celled, cube-shaped eukaryote obtains array number 1. The first generation of this cubic species obtains array number 2 and consists of cube-shaped eukaryotic cells composed of 8 (2^3) unit cubes, the second generation cells with array number 3 are composed of 27 (3^3) unit cubes, and so on (Table 2). It should also be mentioned here that each unit cell continuously burns food in oxygen and the molecular remains of the food are eventually converted into ATP and heat. For an adequate cell temperature, the one-unit cube cell exchanges one metabolic heat unit per time unit with the environment. Thus the first eukaryotic cell with array number 1 exchanges with the environment one heat unit per time unit through 6 identical surface planes. The cubic species with array number 2, consisting of 8 (2^3) unit cells with a total of 24 (6 x

2^2) unit surface planes, needs to exchange 8 (2^3) heat units per unit time. The cubic species with array number 3 are made up of 27 (3^3) unit cubes with a total of 54 (6 x 3^2) unit surface planes for exchanging 27 (3^3) heat units per unit time. The important outcome of the growing cube-shaped eukaryote is that the number of heat units to be exchanged per time unit increases by its cube, whereas the number of unit surface planes increases by its square (Table 2). In other words, a characteristic of the development of this eukaryotic live is that an increase in mass is associated with a rise in body mass temperature.

		Total cube	
Growth of cubic species	**Number of unit cubes**	**Required number of heat units to exchange**	**Number of unit-cube surface planes**
Original cube	1	1	6
First generation	8 (2^3)	8 (2^3)	24 (6 x 2^2)
Second generation	27 (3^3)	27 (3^3)	54 (6 x 3^2)
Third generation	64 (4^3)	64 (4^3)	96 (6 x 4^2)
Fourth generation	125 (5^3)	125 (5^3)	150 (6 x 5^2)
Fifth generation	216 (6^3)	216 (6^3)	216 (6 x 6^2)
Sixth generation	343 (7^3)	343 (7^3)	294 (6 x 7^2)
Seventh generation	512 (8^3)	512 (8^3)	384 (6 x 8^2)

Table 2: *Thought experiment of multi-celled development of a single-celled, cube-shaped eukaryote cell, which grows in a Cartesian coordinate system with the same speed in all three directions, and exchanges with its environment per unit-cell one heat unit per time unit.*

To prevent overheating caused by an increase in body mass, natural selection resulted in species whose basal metabolic rate grew at a slower rate than the body mass. The slower rate was achieved by a time-dependent reduction in the cell membrane UI, while membrane bilayers showed essentially no change in the percentage of saturated acyl chains with changes in species size. So the membrane bilayers of small mammals were generally high in docosahexaenoyl chains (C22:6 n-3) and low in oleyl chains (C18:1 n-9), and the opposite was observed in large mammals [13]. A telling example of body core temperature regulation during the evolution period from mouse to *Homo sapiens* is the reduction in the skeletal muscle percentage of docosahexaenoyl chains (C22:6 n-3) from approximately 30% to 2% in parallel with a body mass increase ranging from approximately 10 grams to 85,000 grams [13]. Besides skeletal muscle, heart, liver, and kidney tissue phospholipids have also exhibited allometric trends.

The reduction in docosahexaenoyl chains lowers the membrane flexibility, which in turn, reduces the amount of all functional Class I glucose transporters, and thereby reduces the transmembrane glucose flux. That means endogenous temperature variations modulate the phospholipid fatty-acyl chain composition of mammalian organisms, which indicates a causal relationship between the two variables UI and heat production.

Also the mass-specific metabolic rate of birds depends on the relative balance between mono-unsaturated and polyunsaturated acyl chains in membrane bilayers [13]. Thus there is strong evidence that the slow-down principle is conserved universally across eukaryotic life - say, during nearly 2 billion years of evolution. In summary, adaptive thermogenesis occurs in all warm-blooded species [8,14].

Today, a human parallel of this evolutionary principle still occurs during a pregnancy, i.e. an increase in maternal mass and a temperature rise by roughly 1°C generates a reduction in the maternal UI. A reduction in UI lowers the maternal membrane flexibility, which in turn, reduces the amount of all functional Class I glucose transporters, and thereby increases the maternal plasma-glucose concentration and insulin level. The well documented data of appreciable increases in fasting serum insulin levels and free fatty acid concentrations during pregnancy support the hypothesis of the slow-down principle [15-17]. All in all, a fine example of a status of short-term heat acclimation.

In a previous study, we discussed that exercise training increases the conversion of white fat into brown adipose tissue. Brown adipose tissue consists of more saturated fatty-acyl chains, compared to white fat. So burning brown fat lowers the concentration of saturated free fatty acids, which in turn, leads to an increase in membrane flexibility and thereby promotes the transmembrane glucose flux [18].

Heat production and its relevance in type 2 diabetes

Mitochondria are the powerhouses of the eukaryotic cells. They are surrounded by a simple outer membrane and a more complex inner membrane. The space between these two membranes is referred to as the intermembrane space and the space surrounded by the inner membrane as the matrix. The four protein complexes of the respiratory chain are embedded in the inner mitochondrial membrane, together with the enzyme ATP synthase and the uncoupler proteins (UCPs) [19].

To understand a possible scenario for a causal relationship between heat production and the onset of type 2 diabetes mellitus, you will find here a brief synopsis of the concept of the eukaryotic cellular energy transport system. Hydrogen is the energy carrier par excellence for the energy saved in our food. After absorption of our food, hydrogen is being stripped from the molecular remains of these nutrients, and passed via the citric acid cycle into the first protein complex, complex I, of the four distinct mitochondrial respiratory protein complexes. Although the precise mechanism is not known, complex I rids the electron of its energy carrier hydrogen, which results in a proton (H^+). The electrons are drawn onwards in the respiratory chain to the ultimate electron acceptor oxygen to form H_2O. For each pair of electrons stripped from food, ten protons are ferried across the inner mitochondrial membrane into the intermembrane space that builds up a proton gradient across the inner mitochondrial membrane with an electrochemical potential of ~200 mV. The protons present in the intermembrane space can re-enter the matrix through the inner membrane in two different ways.

The most famous road of this return is through the mitochondrial enzyme complex ATP synthase. Its F_0 complex forms the transmembrane channel through which protons move to drive ATP synthesis. Via an alternative way protons, uncoupled from mitochondrial ATP production, can re-enter the matrix through the pore of uncoupling protein UCP1 without using energy for any purpose, and dissipate their potential energy as heat [19]. Although UCP1 has an unchallenged and evident thermogenic effect, a consensus concerning its mode of action and the control of its functional activity has not yet been reached.

Experimental data of intracellular temperature mapping, based on a novel fluorescent polymeric thermometer and fluorescence lifetime imaging microscopy, demonstrated clearly the existence of mitochondrial-mediated heat production [20]. This heat production was observed as a proximal local temperature increase. It could be concluded that the local temperature near the mitochondria was higher than the temperature of the rest of the space in the cytosol (aside from the centrosome). Furthermore, this local heat release from mitochondria is accelerated when ATP synthesis is stalled by an uncoupling reagent [21]. Despite incomplete understanding of the uncoupling functions for maintaining energy homeostasis, all this suggests that, in healthy subjects, a balance exists between the amount of mitochondrial intermembrane-space protons, which re-enter the matrix through the ATP synthase for driving ATP synthesis on the one hand, and the amount of mitochondrial intermembrane-space protons, which re-enter the matrix through UCP1 and releasing their energy as heat on the other.

Now we are able to discuss the consequences of a hypothetical genetic anomaly, which shifts the existing equilibrium of proton transport between these two pathways in the direction of UCP1. More specifically, we hypothesize a status of an increased flux of intermembrane-space protons through UCP1 to the matrix, which causes hyperthermia (Figure 1). To keep the body core temperature within the narrow range compatible with live, the slow-down principle enters into force. This principle leads to an appreciable reduction in UI of membrane phospholipids, and thereby lowers the membrane flexibility and reduces the amount of all functional Class I glucose transporters.

These phenomena represent a blueprint of the presence of type 2 diabetes in human individuals. Recall that Kelley et al. reported impaired functional capacity and morphological alterations of mitochondria obtained from the *vastus lateralis* muscle of volunteers with type 2 diabetes [22]. The observations of reduced activity of rotenone-sensitive NADH:O_2 oxidoreductase, a smaller mean size of mitochondria with a less clearly defined internal membrane structure, and smaller cristae are in line with the hypothesis that type 2 diabetes is a status of long-term heat acclimation.

Conclusions

To my mind, at least, the updated scheme of the onset of type 2 diabetes as a status of long-term heat acclimation makes a great deal of sense, which potentially sheds new light on the pathogenesis of type 2 diabetes. The refined working hypothesis describes the simplest possible scenario for the development of this disease and is compatible with a vast amount of published data in this area. A status of long-term heat acclimation leads to an appreciable and lifelong reduction in UI [23,24]. A reduction in UI lowers membrane flexibility, which in turn, reduces the amount of all functional Class I glucose transporters, and promotes tissue hypoxia. These items might be the main cause of hyperglycemia, and the onset of vascular and neurological lesions in type 2 diabetes. The new light on the pathogenesis of type 2 diabetes means that antihyperglycemic agents control glycemia without influencing the UI, while exercise in combination with diet largely restores [25] the transmembrane glucose flux through raising the UI. It is advisable for physicians to lay emphasis not only on glycemic outcomes but also on prevailing UI levels of individuals with type 2 diabetes or with high risk for type 2 diabetes.

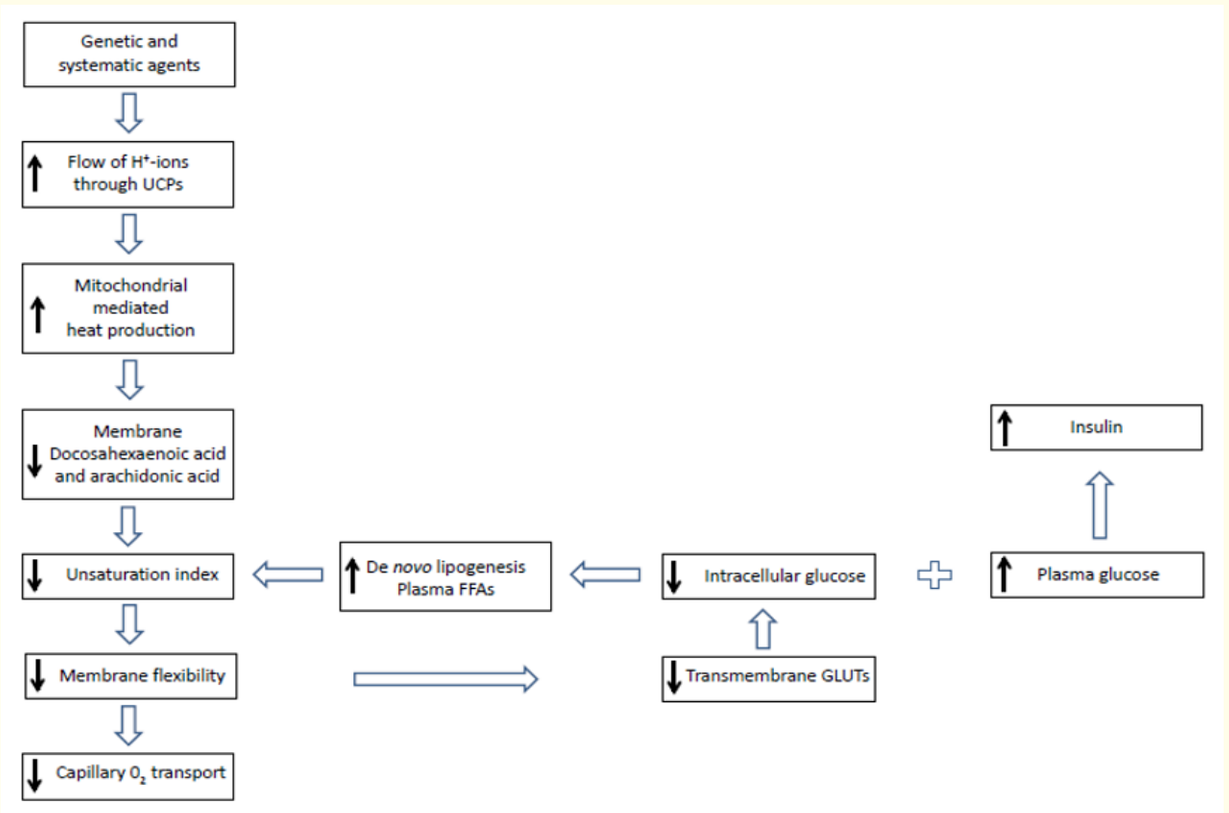

Figure 1: *Although the results of genome-wide screen for type 2 diabetes susceptibility genes are still being debated, a refined working hypothesis proposes that the primary effect of the involved genes generates an increased flux of mitochondrial intermembrane-space protons through UCP1 into the matrix, which causes an increase of extra heat. This process initiates the slow-down principle.*

UCP: Uncoupling Protein; FFA: Free Fatty Acid; GLUT: Glucose Transporter.

In a previous study, we discussed the beneficial effect of exercise on membrane flexibility, and the importance of the assessment of UI [26]. The benefit of exercise is the increased demand for ATP synthesis. Exercise activates the transcription of the genes, which encode the components of ATP-synthases for the production of extra molecules ATPase, whereas it leaves alone the transcription of the UCP1. That may generate a shift in the balance of protons escaping through the UCP-channel and the ATPase channel, in favor of the latter, which ameliorates the status of long-term heat acclimation.

Now we have summarized the current knowledge about cell membranes, we can answer the question: What went wrong with the animal models for dissecting the underlying mechanisms of type 2 diabetes? [27]. When selecting a model, one of the issues that should be considered is whether it reproduces the major clinical symptoms of type 2 diabetes. There is increasingly powerful evidence to support the suggestion that the mean feature of type 2 diabetes is a status of long-term heat acclimation characterized by a reduction in UI. However, the used models are based solely on the principle that they reproduce a status of progressive development of insulin resistance and lack of appropriate compensation by the β-cells leading to a relative insulin deficiency [28]. This is probably the number one reason for the growing awareness of the limitations of some widely used animal models in type 2 diabetes research.

A surprising result of our thought experiment with the growing cube-shaped eukaryote is the required number of heat units, which should be exchanged per time unit, increases by its cube, whereas the number of unit surface planes increases by its square. The consequences of overheating should be functional decline of mitochondria. A way out is to restrict the required number of heat units, which should be exchanged with the environment. In mathematics, this can be realized by multiplication the exponential value 3 (Table 2, 3th column; required number of heat units) by the value 2/3. It should be noted that for all generations of the original cubic species this operation results in the value 2. In that way, the different generations of cells will mimic the heat exchange profile of the eukaryotic one-unit cell. For example, the cubic species with array number 4, which is made up of 64 (4^3) unit cubes with a total of 96 (6 x 4^2) unit

surface planes, needs to exchange 64 (4^3) heat units per unit time (Table 2). After multiplying the exponent value 3 of the required number of 64 (4^3) heat units, which should be exchanged, by 2/3, each of the remaining 16 heat units have at their disposal 6 out of 96 unit-cube surface planes for heat exchange, which mimics the situation of the original single-celled eukaryote. This methodology is applicable to all generations. Of note, the found correction factor value 2/3 is almost identical to the allometric coefficient of 0.69, which is based on relevant data from the literature for 619 species with masses that ranged from 3-300,000g [11]. This result underlines that the thought experiment is a reliable representation of the slow-down principle.

So apparently, if we want to cure type 2 diabetes, we have to find a genuine solution for lowering the increased amount of mitochondrial intermembrane space protons, which re-enter the matrix through UCP1. For the moment, however, that search will be hampered because of an accord of the definition of an uncoupling protein has yet not been reached, a consensus concerning the mode of action of UCP1 and its functional activity has also not been reached, and a high-resolution 3D crystal structure of UCP1 is not yet available [29]. However, knowledge and understanding of the presented issues are essential for informing public health programmes and policy, based on the expectation that these concepts will affect governmental decision-making regarding public health issues.

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