Insulin resistance in an energy-centered perspective

Ping Wang, Edwin C.M. Mariman *

Department of Human Biology, NUTRIUM, Maastricht University, Postbus 616, 6200MD Maastricht, the Netherlands

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Abstract

Insulin resistance, of which the incidence is dramatically increasing in Western societies, is usually regarded as a pathological condition. However, arguments can be provided that insulin resistance may be a normal physiological mechanism to let cells and organs deal with the competition for various sources of energy, especially under circumstances of energy stress. Here we review four different hypotheses dealing with insulin resistance: the glucose-fatty acid cycle, the ER and oxidative stress response, the selfish brain, and the thrifty/not-so-thrifty genotype. Each hypothesis has a specific view on insulin resistance, but they also can complement each other. Combining the four hypotheses supports the view that physiological insulin resistance is indeed one of the adaptive regulation mechanisms, which has benefit for survival of the organism by restoring and maintaining the energy balance at the cellular and organism level. In principle insulin resistance seems to be a reversible physiological trait implying that there may be a specific mechanism to down-regulate insulin resistance once the energy balance is regained. The combined model also describes several ways, by which insulin resistance is promoted during prolonged increased energy supply. A better understanding of the complex background of physiological insulin resistance and of the nature of its regulatory mechanisms will be valuable for the treatment of pathological insulin resistance and type 2 diabetes. The present review may be helpful for this.

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1. Introduction

Insulin is an important anabolic hormone that mainly regulates glucose homeostasis in mammals, but similar molecules and signaling pathways are evolutionary conserved in lower organisms [1]. Nowadays, the reduced insulin action in the body referred to as insulin resistance, reaches an epidemic level in humans. In Europe, the prevalence of insulin resistance as indicated by impaired glucose homeostasis is about 15% in middle-aged people and 35–40% in the elderly [2]. Insulin resistance is a defect typically preceding type 2 diabetes. A conservative estimation indicates that the global prevalence of diabetes, of which over 90% is type 2 diabetes, will be 4.4% in 2030 [3].

Together with the rapidly increasing epidemic of insulin resistance and type 2 diabetes, there is an epidemic of obesity and numerous studies have shown that these two are linked. The degree of obesity is non-linearly related to insulin action [4]. However, lean people can be insulin-resistant and not all insulin resistance is attributable to obesity. Epidemiological studies in the United States and Europe all pointed out that obesity accounts for about 25% of variability in insulin resistance [5,6]. The prevalence rates of insulin resistance in the lean, overweight, obese and extreme obese non-diabetic population was 10%, 26%, 34% and 60%, respectively [5]. Since obesity is due to a positive energy balance, the association of insulin resistance with obesity indicates that insulin resistance is related to the energy metabolism.

Insulin resistance occurs in the insulin target organs, mainly adipose tissue, muscle and liver. Using tissue-specific insulin receptor knockout mouse models, it has been shown that the disturbance of insulin signaling pathways in adipose tissue or in muscle only causes local insulin resistance, but that this in liver can cause severe systemic insulin resistance [7]. It points out the critical role of liver in the development of insulin resistance. In addition, the knockout of the insulin receptor in brain caused...
mild systemic insulin resistance, which was accompanied by obesity [8]. In humans there is no clear evidence yet indicating which organ is the initial site of systemic insulin resistance.

Although insulin resistance is mostly regarded as a pathological condition, similar to type 2 diabetes, only one third of the subjects with insulin resistance will develop type 2 diabetes [9,10], in which the insulin secretion is insufficient due to limited compensatory growth of islets and to increased necrosis [11]. Here we provide information that in principle insulin resistance is a normal physiological adaptive response to energy stress. Four models have already been raised that support our notion: the glucose-fatty acid cycle, the endoplasmic reticulum (ER) stress response, the selfish brain theory, and the thrifty genotype.

2. Fuel competition: the glucose-fatty acid cycle

Glucose and lipids (fatty acids and ketone bodies) are the major sources of energy for the body [12] and for long it has been noticed that there is competition for respiration between these fuels [13]. Already in 1963 Randle and colleagues presented their theory, the so-called glucose-fatty acid cycle, on the interactions between these two major fuels to explain insulin resistance. The original theory proposed inhibiting interactions between glucose and fatty acid metabolism in muscle and adipose tissue, and also included their cooperative interaction for lipogenesis [14]. The inhibitory interactions are that 1) uptake of glucose by adipose tissue inhibits the lipid flow to muscle by inhibiting the release of fatty acids from adipose tissue and by inhibiting the formation of ketone bodies by the liver, and that 2) increased supply of lipid fuels inhibits glucose uptake, activation and oxidation in muscle. These interactions constitute a mechanism beyond hormonal regulation for controlling circulating glucose homeostasis, although hormones like insulin, growth hormone, corticosteroids and adrenaline, modify the control.

In the following studies this hypothesis has been further developed with focus on the respiratory competition between glucose and fatty acids and it was also expanded to include more functions of other organs such as liver and pancreas. After 35 years, Randle reviewed the glucose-fatty acid cycle and made it clear that the principle two sides of the cycle are: 1) the provision of glucose promotes glucose oxidation and glucose and lipid storage, and inhibits fatty acid oxidation, 2) the provision of fatty acids promotes fatty acid oxidation as well as fatty acid and (when available) glucose storage, and inhibits glucose oxidation [13]. Insulin is the key player in the cycle (Fig. 1). The inhibitory effect of glucose on fatty acid oxidation is achieved through inhibition of carnitine palmitoyltransferase-1 (CPT-1) by malonyl-CoA [15], which results in a down-regulation of the transport of activated fatty acids into the mitochondria for oxidation. The inhibitory effect of fatty acids on glucose metabolism is achieved through inhibition of the pyruvate dehydrogenase (PDH) complex by increased mitochondrial ratios of acetyl-CoA/CoA and NADH/NAD [13], and also through other lipid intermediates that suppress insulin signaling pathways such as long-chain acyl-CoA, beta-OH-butyrylcarnitine and ceramide [16].

Despite the mutual inhibition of oxidation, glucose and fatty acids also show their complementation. Glucose stimulates lipid storage directly by offering glycerol-3-phosphate for triglyceride synthesis and indirectly by the inhibiting effect of insulin on lipolysis. In addition, fatty acids may stimulate hepatic glucose output at low insulin status. This has been interpreted as to mainly ensure preferential use of glucose when available and preservation of fat storage [12].

The principle of the hypothesis is evidenced by numerous studies in both humans and animals [13]. It is of importance for normal physiology and also can provide a possible explanation for insulin resistance. According to this theory, a state of insulin resistance can be reached when an excess of fatty acids and ketone bodies released by adipose tissue and to some extent by muscle, reduces glucose utilization via inhibiting glucose uptake, glucose oxidation and glycogen synthesis, and enhancing gluconeogenesis. Consistent with this theory, obese people, normally with a high plasma non-esterified fatty acids concentration [17], have higher risk to develop insulin resistance [18,19]. In fact, this theory has been intensively and successfully applied in constructing a human in vivo insulin resistance model by intravenous triglyceride infusion [20]. The evoked insulin resistance will disappear after ceasing the infusion. This lends support to the idea that insulin resistance is a normal reversible physiologic reaction related to the type of fuel supplied to the tissue. However, care should be taken here, because it has been reported that impaired insulin-stimulated glucose uptake may be more related to reduction in glycogen synthesis than in glucose oxidation [21].

It has been repeatedly observed that the inhibition of fatty acids oxidation by blocking CPT1 activity improves systemic insulin sensitivity [22–24]. Preventing fatty acids from entering the mitochondria allows glucose to be oxidized. This suggests that the competition for oxidation between the fuels is based on the limitation of the mitochondrial oxidative capacity. It seems reasonable that in certain cell types and under certain circumstances...
mitochondrial oxidative capacity should be limited to keep the energy production in line with the actual needs, a matter of energy economy. The selection of which fuel is to be oxidized may depend on the ratio of their availability and on the type of tissue.

Obviously, the glucose-fatty acid cycle is not the only mechanism regulating fuel consumption. Under low energy conditions with depletion of ATP, increased glucose uptake and fatty acid oxidation can happen simultaneously as a consequence of the activation of AMP-activated protein kinase (AMPK) [42]. In this sense, AMPK serves as a mediator to counteract cellular energy stress. It triggers signaling cascades that restore the cellular energy level by suppressing ATP consuming pathways and activating ATP generating pathways. In muscle, stimulated pathways include both pyruvate oxidation and fatty acid oxidation via mitochondrial biogenesis [46].

In summary, under conditions of sufficient energy supply, the fuel competition between glucose and fatty acids plays an important role in normal physiological conditions to maximize energy economy. The competition may be based on the limited mitochondrial oxidative capacity of tissues. Supply of fatty acids inhibits glucose utilization inducing a reversible state of insulin resistance. Prolonged impaired glucose metabolism by over-active lipid utilization may lead to non-reversible insulin resistance and type 2 diabetes.

3. Cellular stress response: ER stress and oxidative stress

Insulin-like peptides including insulin and insulin-like growth factor 1 (IGF-1), are evolutionary conserved from invertebrates to mammals. Interestingly, in nematodes and flies, a defect in insulin-like signal transduction increases longevity [27]. In defective insulin/IGF-1 signaling pathways the important mediator is the activation of proteins of the forkhead transcription factor family (FOXO). Normally, via the protein kinase AKT insulin/IGF-1 signaling pathways lead to the phosphorylation of FOXO, inducing their movement to the cytoplasm and causing their deactivation and degradation. By contrast, stress stimuli activate FOXO via phosphorylation on different sites by Jun-N-terminal kinase (JNK) [28]. Activated FOXO proteins can counteract the signals of insulin as for instance by stimulating gluconeogenesis [29,30]. In the nucleus they up-regulate a series of target genes, thereby promoting cell cycle arrest, apoptosis, or stress resistance [28]. Stress resistance is highly coupled with longevity. A defect of the insulin-like receptor DAF-2 induces activation of the FOXO protein DAF-16 and results in long-lived C. elegans but also increases resistance to oxidative stress (by SOD and catalase), heat shock (by chaperones) and UV radiation [31]. Inhibition of insulin/IGF-1 signaling pathway, thus activating the FOXO pathway, showed an alpha-spectrum of stress resistance in long-lived Drosophila [32]. In mammals, the association of reduced insulin/IGF-1 signaling with increased longevity is not so clear. At least in part this is due to the much more complex endocrine cross talking between the insulin/IGF-1 system and sex hormones, thyroid hormone and growth hormone [33]. Also, in mammals the insulin and IGF-1 signaling pathways operate more separately with the insulin effect more on metabolism and the effect of IGF-1 more on growth. Although mutating the IGF-1 receptor generates long-lived mice with increased resistance to oxidative stress [34], and although the polymorphism on IGF-1 receptor gene in humans may affect longevity [35], there is no decisive evidence yet that decreased insulin signaling in humans is linked to life span.

The evidence described above shows that insulin signaling antagonizes JNK/FOXO signaling and vice versa. In Drosophila, increased JNK/FOXO activity represses systemic insulin signaling mainly at the level of insulin production [36]. In line with this view, a function of insulin resistance in stress resistance has been proposed recently. Özcan, Hotamisligil and colleagues demonstrated that endoplasmic reticulum (ER) stress plays an important role in insulin resistance [37,38]. ER is the organelle for protein biosynthesis and post-translational modification that is especially crucial for secreted proteins. Cellular redox change, deprivation of glucose, abnormal Ca^{2+} concentration, viral infection, overflow of lipids, increased secretion activity, and expression of mutant proteins all pose stress on the ER. Adaptively, ER stress induces a corresponding response to restore the homeostasis by decreasing the biosynthesis of new proteins, enhancing expression of chaperones for protein folding, and increasing proteolysis for misfolded proteins [39,40]. In both genetic (ob/ob) and diet-induced obesity mouse models, ER stress, as measured by ER stress response markers, predominantly occurred in the liver and adipose tissue [38]. The origin of this ER stress is not clear but increased lipid influx and increased protein synthesis and secretion are suspected candidates. The ER stress activates JNK and subsequently inhibits insulin receptor substrate 1 and AKT both in vitro and in vivo [38]. The insulin resistance can be reversed as shown by the treatment of obese and diabetic (ob/ob) mice with chemical chaperones which reduces ER stress and at the same time also restores the systemic insulin sensitivity [37]. Although the ER stress theory was originally meant to link obesity and insulin resistance, any other reason that causes ER stress may also initiate insulin resistance. This complies with the fact that not all insulin-resistant people are obese. With respect to the question of why insulin resistance is part of the ER stress response, it has been speculated that it implies an as yet unidentified, but evolutionary conserved advantage to cells by suppressing anabolic activities and energy flux [38]. We have found that a high concentration of insulin enhances the general secretion of proteins from 3T3-L1 adipocytes [41]. This places the cells under high metabolic stress sensed by the ER. Subsequently, a repression of the insulin signaling may reduce the secretion activity and help the cells to sustain the stress and survive.

Comparable to the ER stress theory, Erol hypothesized that insulin resistance is an evolutionary component of the oxidative stress response [42]. Oxidative stress can be generated by hyperglycemia [43] and for long time it has been accused to cause insulin resistance [44,45]. It was proposed to act as a negative cycle in which free radicals deteriorate insulin action causing hyperglycemia, which in turn causes more oxidative stress. The importance of oxidative stress in the development of insulin resistance might be revealed through anti-oxidant treatment. However, such human studies have generated contradictory results [46,47]. In Erol’s view, insulin resistance is a physiological adaptation. In response to oxidative stress, an
insulin-resistant status may decrease the glucose influx in the cell and restore the redox homeostasis. However, this hypothesis needs more evidence.

In summary, some conditions including glucose deprivation and lipid overflow may induce ER stress in tissues like adipose and liver. This leads to activation of JNK and FOXO proteins, deactivating IRS-1 and causing insulin resistance. As such, insulin resistance can be seen as a reversible physiologic reaction. Under conditions of hyperglycemia, insulin resistance will alleviate the oxidative stress of the tissues (Fig. 2).

4. Organ competition: the selfish brain

The human brain is the only organ in the body that does not show weight loss during prolonged starvation and malnutrition [48]. This illustrates its primary position in survival and also in nutrition. For survival the brain demands a large proportion of nutrients. Glucose is the preferred fuel but under hypoglycemia ketone bodies and lactate may also be used. In the resting or fasting state, 55% of the body glucose is consumed by the brain [49]. The brain does not have a way to store energy, thus it exclusively depends on glucose supply by the blood flow. To meet this request, the influx of fuel to the brain must have priority in the whole body energy metabolism. Recently Peters, Fehm and colleagues presented the “Selfish brain theory” to describe the mechanisms underlying the competition between brain and peripheral organs for energy resources [50–52]. These mechanisms aiming at brain survival may disturb the peripheral energy metabolism and they propose that obesity and type 2 diabetes may in fact be brain disorders.

In this theory, the brain has two ways to ensure its energy supply: re-allocation of the energy from peripheral body to brain, and intake of energy from the environment. When the concentration of ATP in the brain turns low, a signal in the form of glutamate triggers the astrocytes, which form part of blood–brain barrier (BBB), to open their glucose transporters (GLUT1) for glucose uptake. Simultaneously, the stress system is activated via the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system. This activation leads to the secretion of neuroendocrine factors in the periphery, such as norepinephrine and glucocorticoids like cortisol. Eventually this activation increases the availability of glucose in the blood by stimulating liver gluconeogenesis and inhibiting glucose uptake by muscle and adipose tissue. The peripheral organs switch to lipid oxidation promoted by the increased availability of fatty acids by the stimulation of adipose tissue lipolysis. At the same time the brain also changes the organism’s eating behaviour to take up more nutrients into the body. This is brought about by the activation of the lateral hypothalamus with the release of orexigenic peptides. Leptin and insulin as increased fat storage signals, give feedback from the periphery to the brain to suppress this eating behaviour and keep nutrient intake under control. The brain combines both these strategies to regulate its energy status. Through establishing memories in the limbic system, the brain learns to develop specific patterns of shifting between re-allocation and intake to adapt to various environmental conditions and stress challenges (Fig. 3). The aim of the selfish brain regulation is a constant energy status inside the brain, without respect for the peripheral demands.

According to this theory, it is a fundamental defect in the brain that causes obesity and insulin resistance. A permanently less active limbic (hippocampus/amygdala) system and/or a failure to allocate energy to the brain causes a disturbance of the balance between allocation and food intake behaviour, generating a pattern with more focus on food intake. Consequently, an increase in body weight and also an increase in peripheral insulin sensitivity happen. Then, by the feedback from leptin and insulin, the balance shifts to the other side to promote allocation by the activation of the stress system, so that insulin resistance occurs and the increase of body weight is stopped. As such, insulin resistance represents the attempt to compensate for the original disturbance of the set point in the balance between allocation and intake [50–52].

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A recent large prospective cohort study provided data linking cortisol with progression of obesity, in line with this hypothesis. It was shown that circulating cortisol concentrations are somewhat lower in obese men than in non-obese men, and that the greatest rise in cortisol level occurred among subjects who lost weight during follow-up [53]. Other proof comes from type 2 diabetes patients. HPA axis hyperactivity and limbic memory impairment have both been found in type 2 diabetic patients [54]. In addition, untreated patients decreased their body weight, while strict glycemic control promoted weight gain and did not improve diabetes-related mortality [55].

While the selfish brain theory accuses the disruption of cerebral energy allocation behaviour for causing obesity and insulin resistance, there are other explanations possible that take into account the competition of the brain with the periphery for glucose. One could be the inefficient transport of glucose over the BBB. It is reasonable to suspect that a decreased transport, which cannot match the energy demand of the brain, will initiate the stress system and induce insulin resistance. A decreased glucose transport over the BBB has been confirmed in diabetic rodent models [56,57]. It is mainly explained as an adaptive mechanism for glucose supply to the brain under hyperglycemic circumstances, but in humans no change on glucose transport in BBB was observed for acute or chronic hyperglycemia [58,59]. Diabetic patients with increased plasma glucose concentrations may develop cerebral symptoms of hypoglycemia when their plasma glucose is rapidly lowered to normal concentrations. The symptoms may indicate insufficient transport of glucose from blood to brain [60]. If chronic hyperglycemia, indicating insulin resistance, is not the cause for impaired glucose transport in BBB, then it might still be the consequence. One could speculate here that if glucose transport over the BBB is diminishing with age, as so many other functions of the body, this might be a general cause of peripheral insulin resistance in the elderly by the activation of the stress system.

Another situation in which the brain induces insulin resistance is when the peripheral glucose consumption is so high that it tends to lower the circulating glucose level. It is known that glucose is the main fuel for the immune system [49]. Under conditions of chronic inflammation, the peripheral energy/glucose demand increases such that it may form a competing force against the brain. Since obesity is regarded as a state of chronic inflammation [61], the selfish brain might be the link between obesity and insulin resistance.

Some observations are more difficult to explain by the selfish brain theory. This includes the beneficial effect of physical activity on insulin resistance. By exercise muscle consumes much more energy including glucose thus posing energy stress on the brain. In contrast to the prediction, peripheral insulin resistance is reduced. However, physical activity may shift the balance from allocation to nutrient intake.

In summary, the brain may play a dominant role in directing glucose flux and food intake. Under normal conditions re-allocation of glucose involves peripheral insulin resistance as a normal reversible physiologic regulatory measure. The periphery must be able to give feedback. Hormones like leptin and insulin as well as physical exercise are involved here. A chronic unbalance of the cerebral regulation pathways may cause obesity and persistent insulin resistance. However, this hypothesis was proposed recently and more evidence from different groups is needed to verify its value.

5. Evolutionary view: the thrifty and not-so-thrifty genotype

It has been strongly supported that insulin resistance and diabetes have both a genetic and environmental basis [62]. The heritability estimates for insulin resistance related features can reach 0.72 to 0.78 [63]. Environmental changes play a key role in the fast increasing epidemic of insulin resistance and diabetes, possibly by uncovering genetic factors that may promote insulin resistance. Its high prevalence suggests that the genetic factors have been evolutionary conserved in humans and therefore should have had an advantage for the species. The most famous explanation for such an advantage in humans is the “Thrifty genotype” proposed by James Neel in 1962. The basis of his theory was that our hunter–gatherer ancestors should be able to efficiently store energy during a feast period and survive a subsequent famine period [64]. He suggested that in humans the quick insulin trigger made it possible to rapidly preserve glucose in the body and minimized the loss of this precious nutrient in urea. However, this trait now turns out to be a disadvantage in the Western civilization where food supply is always plenty. The mechanism to trigger a fast insulin response would be over-stimulated with insulin resistance and pancreas exhaustion as a consequence, finally leading to type 2 diabetes. In African American women, the higher prevalence of obesity and type 2 diabetes than in white American women is accompanied by a greater acute insulin response [65]. This may support that the quick insulin trigger is the original event leading to insulin resistance. Later this hypothesis was updated with the increased knowledge on type 2 diabetes. It was pointed out that the original emphasis on the feast-famine influence was over-simplified. In reality, a complex physiological change of the human body might have occurred from stone age to industrial age, a period in which the daily energy expenditure dramatically decreased [66].

Neel’s thrifty genotype theory invoked the attention for an evolutionary benefit of insulin resistance. For this, Reaven’s “not-so-thrifty” genotype hypothesis gave a strong argument. The primary event in Reaven’s theory is insulin resistance instead of the quick insulin trigger. The function of insulin resistance was proposed to maintain muscle mass [67]. Experimental results support that insulin signaling pathways not only promote glucose consumption but also inhibit proteolysis, and that those pathways are divergent because in type 2 diabetic patients the former pathway is insensitive while the latter is still active [68]. According to Cahill et al. [69] the preservation of muscle mass is an advantage to survive famine because of a higher success rate to hunt again. However, during fasting the low insulin level may allow muscle protein to be used for gluconeogenesis to produce glucose for the brain. Reaven thus proposed that systemic insulin resistance is intended to decrease the muscle glucose uptake, saving the glucose for the brain. At the same time the increased blood glucose lowers the demand for muscle proteolysis intended to
support gluconeogenesis. As a consequence, the muscle mass is spared and the individual has a high chance to survive the famine. It was further postulated that muscle insulin resistance would be amplified in modern life by the increased life span, food intake and decreased physical activity, and finally this would cause β-cell failure and type 2 diabetes [67]. The above two hypotheses look at the situation from a different angle. The thrifty genotype theory focuses on the physiological behaviour in the feast period, while the not-so-thrifty genotype theory focuses on the famine period (Fig. 4). Nevertheless, the general idea here is the physiological advantage of hyperinsulinaemia/insulin resistance on survival.

The pre-historic genotype has been evolutionary conserved in modern humans. Healthy, lean, insulin sensitive humans still display the physiological response to short-time starvation (36–72 h) with temporary insulin resistance [70–72]. This implies that insulin resistance is a physical adaptation to energy stress and can be regulated temporally. It suggests that in individuals, who develop persistent insulin resistance and eventually type 2 diabetes despite the “thrifty” or “not-so-thrifty” genotype, there is a defect of the mechanism to reverse insulin resistance under conditions of a surplus supply of energy. This defect can either be acquired or genetic.

In summary, our pre-historic genome has developed to provide the individuals with increased chances to survive famine using temporary hyperinsulinaemia or insulin resistance. Insulin resistance may ensure sufficient glucose for the brain and preserve muscle mass. Under the high nutrition supply of the modern society a defect in the reversing mechanism may render insulin resistance more persistent.

6. Conclusions and perspective

We reviewed here four different theories on the etiology of insulin resistance. Each hypothesis has a specific view on insulin resistance, but they also support the general idea that insulin resistance is a normal physiologic reaction and that persistent energy stress leads to pathological insulin resistance. According to these four hypotheses insulin resistance is a protective adaptation to avoid biological damage on organelle, cell, organ and whole organism level. Several aspects of these hypotheses complement each other and can be put in a model to describe the behaviour of an organism, let it be human, under different conditions of energy supply.

Under conditions of poor nutrition, the human body can rely on its evolutionary selected not-so-thrifty genome and install insulin resistance to preserve muscle mass and at the same time supply the brain with sufficient glucose. According to the selfish brain theory, the latter can be accomplished by shifting the set point in the balance between glucose re-allocation and food intake. Re-allocation via activation of the HPA axis and the sympathetic nervous system will inhibit the uptake of glucose by peripheral organs and at the same time will lead to the release of fatty acids from adipose tissue. According to the glucose-fatty acid cycle, insulin resistance is installed to shift the competition for the mitochondrial oxidation capacity in favor of fatty acid oxidation, leaving the glucose available for uptake by the brain. Tissues with a high proliferation or secretion activity like adipose tissue and liver will sense the poor supply of energy as ER stress and lower their glucose uptake via the Akt–FOXO–JNK interactions. As soon as the supply of nutrition normalizes, insulin resistance is no longer needed.

Under conditions of rich nutrition, the body can rely on its thrifty genome with quick insulin triggers to channel glucose to brain and peripheral organs where the competition with fatty acids for the oxidative capacity is now in favor of glucose. Using glucose as the basis for glycerol-3-phosphate adipose tissue takes up the fatty acids and stores them as triglycerides.

If conditions of high energy supply continue for longer times, insulin resistance may become persistent through various mechanisms. Prolonged storing of fatty acids requires proliferation of the adipose tissue. In addition, high insulin levels will exhaust the secretory activity of adipocytes. Together this will generate ER stress that will promote insulin resistance as a protective measure. With body weight reaching the obese state, a process of chronic inflammation occurs that competes with the brain for glucose. The selfish brain will react by activating a response through the HPA axis, the more while high levels of insulin and leptin will help to shift the balance set point towards allocation of glucose. This will again promote the persistence of insulin resistance in tissues like muscle and liver. Finally, a reduction in the permeability of the BBB may also promote peripheral insulin resistance to increase the blood glucose level and prevent hypoglycemia of the brain.

Combining the four hypotheses supports the view that physiological insulin resistance is one of the adaptive regulation mechanisms, which has benefit for survival of the organism by restoring and maintaining the energy balance at the cellular and organism level. In principle it seems a reversible trait implying that there may be a specific mechanism to down-regulate insulin resistance once the energy balance is regained. Further, the combined model describes several ways, by which insulin resistance is promoted during prolonged increased energy supply. Yet, a defect...
in the proposed down-regulating mechanism may be necessary to let insulin resistance persist and turn it into a pathological condition. A better understanding of the complex background of physiological insulin resistance and of the nature of its regulatory mechanisms will be valuable for the treatment of pathological insulin resistance and type 2 diabetes. The present review may be helpful to accomplish this.

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