Opinion paper

The evolutionary benefit of insulin resistance

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SUMMARY

Insulin resistance is perceived as deleterious, associated with conditions as the metabolic syndrome, type 2 diabetes mellitus and critical illness. However, insulin resistance is evolutionarily well preserved and its persistence suggests that it benefits survival. Insulin resistance is important in various states such as starvation, immune activation, growth and cancer, to spare glucose for different biosynthetic purposes such as the production of NADPH, nucleotides in the pentose phosphate pathway and oxaloacetate for anaplerosis. In these conditions, total glucose oxidation by the tricarboxylic acid cycle is actually low and energy demands are largely met by fatty acid and ketone body oxidation.

This beneficial role of insulin resistance has consequences for treatment and research. Insulin resistance should be investigated at the cellular, tissue and whole organism level. The metabolic pathways discussed here, should be integrated in the accepted and valid mechanistic events of insulin resistance before interfering with them to promote insulin sensitivity at any cost.

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1. Introduction

“Insulin resistance” is generally regarded as a deleterious condition associated with the metabolic syndrome, type 2 diabetes mellitus and critical illness; disorders that lead to hyperglycemia. In turn, chronically elevated glucose levels are causing many of the ill effects of these conditions. Consequently, much effort has been invested into treating hyperglycemia on its own: glucose targets have not only been set for patients with type 2 diabetes mellitus, but also for critically ill patients. In the latter tight glucose control has been advocated until very recently. Likewise efforts have been performed to feed carbohydrates to patients until very shortly before surgery to decrease insulin resistance.

The bad image of insulin resistance has obscured its potential benefits as an adaptive mechanism. Insulin resistance (or the ability to selectively modulate the cellular/tissue response to insulin) is evolutionarily well preserved in insects, worms, and vertebrates including humans. Having been under so much evolutionary pressure, its persistence suggests that it benefits survival of the species. Here we shortly review old and recent experimental evidence regarding the important role of insulin resistance in various states (e.g. starvation, immune activation, growth) to finally hypothesize on the evolutionary importance of insulin resistance.

2. Insulin resistance in starvation

A century ago Benedict demonstrated in his classic work “A study on long term fasting” that the human organism could limit its nitrogen losses during long term starvation. Starvation is accompanied by insulin resistance as shown by targeted inhibition of the action of insulin in oral glucose tolerance tests and clamp studies. Glucose uptake and oxidation are decreased by mechanisms like decreased phosphorylation of insulin signaling intermediates in muscle such as AKT and the AKT substrate 160.3,4 Diminished glucose oxidation has profound impact on intermediary metabolism: during starvation energy production is largely derived from fat and ketone body oxidation. Although it has been suggested that glucose needs to be available for oxidation by the central nervous system during starvation, it has been shown that ketone body oxidation secures most of brain energy requirements under starved conditions.5 Also in critically ill patients energy coverage in the brain must be largely derived from other sources than glucose.6 Meanwhile, diminished oxidation of glucose diminishes the necessity to utilize amino acid carbon skeletons to produce glucose. This minimizes protein losses as described in landmark studies and insulin resistance has therefore been suggested to promote survival, because the total protein content of the body is a major determinant of long term survival in starving individuals.7,8 Only in rare situations, when lipid stores are very low, they may limit
survival. Once they are eroded, only protein is left as oxidizable substrate to yield the necessary ATP. In view of the fact that the amount of calories that can be derived from the oxidation of the available protein in the body is very small compared to fat stores its oxidation will rapidly lead to protein depletion and to death. This phenomenon has been studied at length in the Antarctic King Penguin (Aptenodytes Patagonicus) and is therefore referred to as the King Penguin syndrome.9

Within two days of starvation, glycogen stores are depleted necessitating formation of the necessary glucose mostly from carbon skeletons of amino acids.10 Complete mitochondrial glucose oxidation is minimized, decreasing protein carbon loss. Notably, glucose production from pyruvate and lactate contributes substantially to liver glucose production but no net glucose is produced because lactate and pyruvate originate from the degradation of glucose (Cori cycling).11 Also, production of the gluconeogenic amino acid alanine, by transamination of glucose derived pyruvate and the amino group of glutamate, is modest in starvation but still somewhat higher compared to the postprandial situation.9,12 The subsequent hepatic glucose production from alanine is a similar process as in Cori-cycling.11,13 Altogether, these adaptations limit glucose oxidation in the TCA cycle.

Support for this mechanism comes from the field of FoxO subfamily protein research. FoxOs are regarded as the "long sought insulin-regulated transcription factor responsible for insulin resistance".14 Here, several authors have shown that the transcription factor FoxO1 regulates insulin function.15-16 Increased cellular survival and proteolysis are associated with gain of function of FoxO1, whereas deletion of the expression of the gene shortens life span.15,17 In general, FoxOs are transcription factors that modulate gene expression during development, fasting, stress resistance and calorie restriction-induced longevity. They are a shared part of pathways regulating diverse cellular functions like cell differentiation, metabolism, proliferation and survival.14

3. Insulin resistance in stress starvation

In stress starvation (starvation associated with trauma or illness) most metabolic processes occurring in pure starvation intensify due to higher energy requirements. This energy is largely derived from fatty acid and ketone body oxidation. However, peripheral organs become more catabolic (skin, bone, muscle) resulting in net protein loss with amino acids taken up and utilized in protein synthesis by central organs (liver, spleen, immune cells, healing tissues) for stress responses (e.g. synthesis of acute phase proteins, proliferating immune cells) supporting healing.16 Meanwhile, amino acids are used for glucose synthesis and indirectly for alanine and glutamine which in turn serve to support host response. However, alanine and glutamine also serve partly as precursors of glucose synthesis, which leads to irreversible urinary nitrogen (=protein) loss in the form of urea and ammonia. When alanine is used as precursor of glucose in the liver, urea is obligatorily produced and excreted in the urine. Similarly glutamine used for glucose production in the kidney obligatorily produces NH₃ which is partly excreted in the urine. Amino acids are also important for synthesis of other non-protein products (e.g. neurotransmitters, nucleotides, osmolytes, purines) most of which cannot be fully re-utilized for the synthesis of the carbon skeletons of amino acids.

In stress starvation, insulin resistance is even stronger, limiting glucose oxidation, in turn promoting protein sparing.15 Glycogen synthesis is also inhibited, but rates of glycolysis and gluconeogenesis (Cori-cycling) are increased. This serves other purposes than glucose formation and energy production because in Cori cycling no new glucose is formed and it is an energy consuming cycle. The required energy must come directly from fatty acids or indirectly via ketone bodies because more ATP is needed for the production of glucose than is generated in glycolysis. The increase in glucose requirement in sepsis compared to starvation has generally been ascribed to failure to increase ketone body production and, consequently dependency of the central nervous system on glucose as fuel. The data substantiating this are weak. In septic patients receiving hypocaloric parenteral administration of glucose and amino acids or when completely starving, ketone body production is comparable to starving controls.9 Only during triglyceride infusion ketone body rate of appearance is lower in septic patients than in controls.25 Despite inhibition of glucose oxidation, glucose requirements are increased for other purposes as detailed below, leading to a more rapid protein loss.

4. Glucose serves biosynthetic purposes

In the first step of the oxidative part of the pentose phosphate pathway (PPP), glucose 6-phosphate is partly oxidized via glucose 6-phosphate dehydrogenase, producing the reducing equivalent NADPH. NADPH is necessary to maintain the redox potential of different substrates such as glutathione, but is also required for formation of radicals killing bacteria, and possibly to facilitate phagocytosis, and for fatty acid synthesis.20,21 Further down the oxidative part of the PPP, additional NADPH is formed via 6-phosphogluconate dehydrogenase when forming ribulose 5-phosphate from 6-phosphogluconate. In the non-oxidative part of the PPP ribose-5-phosphate is synthesized for nucleotide synthesis. It is unlikely that there is a fixed ratio between NADPH and ribulose production, because not all ribulose 5-phosphate is used for cell replication. Part of it cycles back to glyceraldehyde phosphate and fructose 6-phosphate which in turn can yield glucose 6-phosphate, completing the cycle.20 Thus, in situations with oxidative stress, lipogenic demand or increased proliferation, increased PPP glucose flux is mandatory.22 Remarkably, the above also applies to cell proliferation and tissue formation during rapid growth as in puberty, pregnancy and cancer as described below.23-25 When cells die by autophagy, apoptosis or necrosis, it is unlikely that products of the degradation pathway of these cells can be fully resynthesized into glucose, leading to net glucose and protein loss.26 This may especially apply to necrosis and to a lesser degree apoptosis, whereas autophagy may be assumed to be regulated in such a way that degradation products can be efficiently re-utilized.

A second pathway in which glucose is used and partly lost, is its utilization as anaplerotic substrate when feeding intermediates into the TCA cycle.27 Here, glycolytically derived pyruvate produces oxaloacetate via pyruvate carboxylase (the major anaplerotic enzyme). This reaction is very distinct from the pyruvate dehydrogenase pathway where pyruvate yields acetyl-CoA for further TCA cycle oxidation or fatty acid synthesis and in which trioses like pyruvate lose a carbon atom, precluding resynthesis into glucose. This latter pathway is blocked in insulin resistant states such as sepsis and starvation as well as in other situations were rapid cell proliferation is required.28,29 TCA cycle intermediates branch off in reactions that are linked to gluconeogenesis, lipogenesis, and the production of substances necessary for cell proliferation like purines, pyrimidines, phospholipids, sterols (cataplerosis).27 When in turn these substances are degraded their carbon skeletons may also not be fully suitable for resynthesis of glucose, which contributes to the net loss of glucose and the necessity for continued formation of modest amounts of new glucose from amino acid carbon skeletons and to an even lesser but still measurable degree from glycerol.30 Only when parenteral triglycerides and amino acids are administered
without glucose in neonates, glycerol has been found to account for more than 50% for the new formation of glucose.\textsuperscript{31}

5. Changes in metabolism during immune response activation (Fig. 1)

Glucose uptake in leukocytes and spleen is enhanced by endotoxin administration, sepsis, trauma, and all other inflammatory conditions. Although leukocytes have a full TCA cycle, they shift from complete oxidation of glucose in the fed non-activated state to glycolysis and increased PPP flux once activated.\textsuperscript{18,21} In Kupffer and endothelial cells, in vitro studies show that glucose flux through the PPP is approximately half of palmitate oxidation and one third of glutamine breakdown.\textsuperscript{32} These findings indicate that in these cells glucose fluxes through pyruvate dehydrogenase (feeding acetyl-CoA into the TCA cycle) and pyruvate carboxylase (to replenish TCA cycle intermediates; anaplerosis) steps are limited as described above. Meanwhile, anaplerosis via glutamine provides a substantial amount of TCA cycle intermediates.\textsuperscript{32} However, the reverse process occurs simultaneously in other cell types in the body (myocytes, adipocytes, brain), in which glutamine is synthesized, employing \(\alpha\)-ketoglutarate from the TCA cycle and amino-nitrogen groups from amino acids (e.g. branched chain amino acids). These cataplerotic reactions can only occur when \(\alpha\)-ketoglutarate is replenished by intermediates of the TCA cycle with glucose derived pyruvate (followed by carboxylation in the pyruvate carboxylase reaction) or by amino acids feeding their carbon skeletons at other sites into the TCA cycle.

In chronic inflammatory diseases like COPD and rheumatoid arthritis, oxidative muscle fibers become partly glycolytic, decreasing glucose oxidation while increasing glycolysis.\textsuperscript{33} Therefore the changes in metabolism described for immune cells are not restricted to the primary site of inflammation and organs considered crucial in the inflammatory response, but may occur in other tissues as well. At the whole body level, qualitative and quantitative changes in glucose flux in the different pathways (e.g. PPP) may be substantial as shown in COPD patients.\textsuperscript{34} The fluxes through these pathways are not exactly quantified and their measurement requires sophisticated techniques.\textsuperscript{35,36}

6. Insulin resistance and growth

Channeling glucose into the PPP and the TCA cycle is also necessary during growth: this has been demonstrated in pregnancy and during lactation.\textsuperscript{37,38} In these conditions dietary carbohydrates are available but glucose is still preferentially used for biogenesis.

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**Fig. 1.** Balance in glucose metabolism in healthy non challenged and challenged circumstances: possible effects on insulin sensitivity. The left panel shows glucose metabolism in the quiescent non challenged state, when no disease/trauma or growth is present. Biosynthesis is low and glucose oxidation and glycogen synthesis are active in the postprandial state. Amino acids from ingested food furnish building blocks for protein synthesis to maintain cell turnover. Green arrows represent glucose derived products for biosynthesis. Burgundy arrows represent pathways of full glucose oxidation. Note production of NADPH and nucleotides. The light blue double arrowed line depicts the bidirectional pathway between PPP and glycolysis. Pathways for \(a\)-citrate mediated glycolysis inhibition and \(b\)-the oxidation of FA and AA are not shown. The right panel shows the shift in metabolism during challenged conditions (trauma, disease, growth, cancer) with the proposed changes in glycolysis, pentose phosphate shunt and citric acid cycle activity. Green arrows represent increased synthesis of cell elements: ribose-5 phosphate, acetyl-CoA (via citrate transport into the cytosol) for FA synthesis, purines, pyrimidines, phosphoethanol pyruvate and glycerol-3 phosphate for phospholipid synthesis. These products serve as substrates for cell proliferation. Amino acids derived from protein breakdown in peripheral tissues (muscle, adipose tissue, skin) serve the same purpose. Burgundy arrows show inhibition of glucose oxidation and glycogen synthesis. Cori-cycling is enhanced in the proliferating state. Note increased pentose phosphate pathway activity for reducing equivalents and nucleotides. Glutamine is another important anaplerotic substrate and is not discussed. The malate-pyruvate shuttle produces NADPH as well (not shown in the figure). The light blue double arrowed line depicts the bidirectional pathway between PPP and glycolysis. Pathways for \(a\)-citrate mediated glycolysis inhibition and \(b\)-the oxidation of FA and AA are not shown. These basic metabolic pathways may be linked to the currently accepted and valid mechanistic events of insulin resistance on the cellular, tissue and whole organism level (e.g. gene expression, insulin signaling, glucose transporters etc). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
To metabolize glucose, pregnant, lactating women and pubertal humans need to secrete increased amounts of insulin, reflecting insulin resistance.39–41

The same mechanisms apply to malignant tumor growth: the well known “Warburg effect” implies that tumor cells rely on glycolysis and fatty acid oxidation.42 Full glucose oxidation is inhibited whereas the flux through the PPP is increased to maintain redox state and (malignant) cell proliferation.26 The malignant cell is able to regulate its own metabolism in this manner and the rapidity of cell proliferation and tumor mass most likely determines the degree of insulin resistance at the whole body level. In the light of the above, the Warburg effect is not restricted to tumor cells but extends to all other situations in which rapid cell proliferation is occurring.43

7. Insulin resistance in obesity

If we accept that insulin resistance benefits limitation of net degradation of protein in long-term starvation and stress while facilitating PPP and anaplerosis, the role of insulin resistance in overfeeding is enigmatic. Accumulation of fat and muscle mass for hibernation (or very likely also for migration) leaves animals severely insulin resistant due to a pro-inflammatory drive induced by abundant amounts of fast as well as to synthesize muscle and fat.44 Similarly, high fat feeding for 11 days in humans results in insulin resistance.45 Obesity and stress starvation share enhanced fatty acid oxidation, inhibition of glucose oxidation and increased Cori cycling. The ratio between glycolytic and oxidative enzyme activities of glucose degradation in obese NIDDM has been found to decrease from obese DMII to obese non-DMII to lean patients and to correlate with insulin resistance.46 The seemingly inefficient generation of energy in cells possessing a full TCA cycle, oxidizing fatty acids while having high glycolytic rates but low glucose oxidation, suggests that cell proliferation, maintenance of the redox state and (malignant) cell proliferation.26 The malignant cell is highly dependent on glucose, whereas the normal cell can use fatty acids. Accumulation of fat and muscle mass for hibernation (or very likely also for migration) leaves animals severely insulin resistant due to a pro-inflammatory drive induced by abundant amounts of fat as well as to synthesize muscle and fat.44 Similarly, high fat feeding for 11 days in humans results in insulin resistance.45 Obesity and stress starvation share enhanced fatty acid oxidation, inhibition of glucose oxidation and increased Cori cycling. The ratio between glycolytic and oxidative enzyme activities of glucose degradation in obese NIDDM has been found to decrease from obese DMII to obese non-DMII to lean patients and to correlate with insulin resistance.46 The seemingly inefficient generation of energy in cells possessing a full TCA cycle, oxidizing fatty acids while having high glycolytic rates but low glucose oxidation, suggests that cell proliferation, maintenance of the redox state and the ability to generate an oxidative burst are prioritized in obesity, besides energy generation and protein sparing.

This proposed chain of events is supported by several publications demonstrating increased PPP activity in experimental obesity.47,48 Only one human related study showed increased PPP activity in vitro in leukocytes from obese subjects.49 Moreover, the relation of these mechanisms with currently accepted and valid mechanistic events of insulin resistance is highly interesting and not mutually exclusive.

8. Evolutionary purpose of insulin resistance

The benefit of insulin resistance in prolonging survival and meeting requirements of tissue proliferation is supported by the finding that in the Drosophila fly insulin sensitivity is upregulated and life span is shortened by knocking out FoxO genes (required to resist amino acid starvation as described above).50 Similar findings have been reported in nematodes and in mice.51 FoxO1 expression combats oxidative stress, preserving cellular function and promoting the switch from carbohydrate to fatty acid oxidation as the major pathway to generate energy during starvation.52 These effects on longevity may be the explanation for the evolutionary development of insulin resistance. However, in obesity related insulin resistance life span is shortened, because chronic energy surplus and hyperglycemia lead to progression of type II diabetes and its complications.

Insulin resistance in trauma or sepsis occurs after the initial hit. This timing explains why interventions such as preoperative oral glucose loading may aid to improved outcome whereas there is still debate about postoperative glucose/insulin treatment.53 Providing the organism with glucose before trauma (i.e. surgery) increases the availability of glucose. Here, glucose is still preferentially used for biosynthetic purposes, but supplying the organism with exogenous glucose decreases the need to produce glucose from endogenous sources (glycogen, amino acids, glycerol) and thereby decreases protein losses. Thus, although studies after surgery demonstrate higher insulin sensitivity compared to the non-glucose supplemented group,52 it will still be lower than in a similar individual who has not been operated on.

In conclusion, although insulin resistant states keep as much glucose available as possible for synthetic and redox regulating functions, it is not exactly known how the fluxes and cycles through the pathways in this network integrate and are actively regulated. At present tools are being developed to describe all metabolic routes that are possible for a group of enzymes. This concept has been used to analyze the interplay between the PPP and glycolysis. The system involves glycolysis, a futile cycle, PPP function and all other pathways within the system that are possible (e.g. accepted pathways of insulin resistance).53,54

9. Hypothesis

Here we hypothesize that insulin resistance promotes glucose availability for the inflammatory response in the defense against starvation, disease and trauma and to promote growth during lactation, pregnancy, puberty and cancer, and in situations where the organism prepares itself for migration or hibernation. This mechanism is evolutionarily well preserved in multiple species, including the human organism. It is also likely that in other insulin resistance states like chronic inflammatory illnesses (chronic obstructive pulmonary disease, rheumatoid arthritis etc.), insulin resistance is initially beneficial in promoting the inflammatory response and healing and not the result of mitochondrial dysfunction.55,56

Insulin resistance is a necessary evolutionary pressure when the main challenges to survival were not obesity and diabetes, rather acute trauma and prolonged fasting. However, in obesity, the ingestion of large amounts of dietary lipid may be adequately dealt with by an initially inflammatory and oxidative stress response and proliferation/growing of fat cells. Chronically, there is a cost that is only partially reversible; then, chronic inflammatory activity and insulin resistance lead to permanent changes/damage that finally result in the well known clinical complications of type 2 diabetes mellitus.

This beneficial role of insulin resistance has consequences for treatment and research. Forcing glucose into oxidative pathways by liberal administration of insulin deprives the organism of glucose for synthetic and anti-oxidative pathways, which is actually suggested by recent findings showing that in ICU patients late initiation of parenteral nutrition was associated with lower insulin infusion rates, faster recovery and fewer complications.57

Moreover, this hypothesis should be tested at the cellular, tissue and whole organism level, integrating these basic metabolic pathways in the currently accepted and valid mechanistic events of insulin resistance. These metabolic mechanisms and their function should be understood before interfering with them to promote insulin sensitivity at any cost.

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Conflict of interest

None.
References


