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Opinion paper

The evolutionary benefit of insulin resistance

Maarten R. Soeters [a,*], Peter B. Soeters [b,**]

[a] Department of Endocrinology and Metabolism, Academic Medical Center, University of Amsterdam, PO Box 22660, 1100 DD Amsterdam, The Netherlands
[b] Department of Surgery, Maastricht University Medical Center, Maastricht University, The Netherlands

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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.

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.[1] 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.[2] 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

* Corresponding author. Tel.: +31 20 5666849; fax: +31 20 6917682.
** Corresponding author. Putstraat 25, 3620 Lanaken, Belgium. Tel.: +32 89245391.
E-mail addresses: m.r.soeters@amc.uva.nl (M.R. Soeters), pb.soeters@maastrichtuniversity.nl (P.B. Soeters).

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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.[8] This phenomenon has been studied at length in the Antartic 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).[7,11] 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.[7,12] The subsequent hepatic glucose production from alanine is a similar process as in Cori-cycling.[7,13] 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.[18] 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 NH_3 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.[19] 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.[6] Only during triglyceride infusion ketone body rate of appearance is lower in septic patients than in controls.[6] 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 macrophages/neutrophils to produce 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