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REVIEWS

Review

Mild Suppression of Hyperinsulinemia to Treat Obesity and Insulin Resistance

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Insulin plays roles in lipid uptake, lipolysis, and lipogenesis, in addition to controlling blood glucose levels. Excessive circulating insulin is associated with adipose tissue expansion and obesity, yet a causal role for hyperinsulinemia in the development of mammalian obesity has proven controversial, with many researchers suggesting it as a consequence of insulin resistance. Recently, evidence that specifically reducing hyperinsulinemia can prevent and reverse obesity in animal models has been presented. Our experiments, and others in this field, question the current dogma that hyperinsulinemia is a response to obesity and/or insulin resistance. In this review, we discuss preclinical evidence in the context of the broader literature and speculate on the possibility of clinical translation of alternative approaches for treating obesity.

Highlights

Insulin acts on multiple tissues to stimulate the synthesis and storage of carbohydrates, lipids, and proteins.

Hypersecretion of insulin is a physiological contributor to diet-induced obesity in animal models.

Obesity can be treated in adult mice following an acute reduction in insulin secretion.

The results of clinical studies are mixed, and additional, more specific manipulations are needed to translate the preclinical knowledge for humans.

Introduction

Insulin is a powerful anabolic hormone secreted from pancreatic β-cells that acts on multiple tissues to stimulate the synthesis and storage of carbohydrates, lipids, and proteins. A lack of appropriate insulin production and secretion, and/or the inability of tissues to adequately respond to insulin, contribute to impaired glucose homeostasis and the pathogenesis of type 2 diabetes [1]. Inappropriate insulin secretion and insulin resistance are also associated with other disorders, such as obesity, atherosclerosis, and hypertension [1–4]. The effects of insulin on glucose homeostasis have been well studied at both the cell biological and whole body physiological levels, but insulin's more potent effects on lipid homeostasis have been studied less *in vivo*. Clinical correlations between **hyperinsulinemia** (see Glossary) and dyslipidemia were already well known [4,5], yet it was only in 2012 when we published on the specific *in vivo* effects of reduced insulin production in the context of obesity prevention that the causal relationship was formally addressed [6]. We have since expanded on these observations to include the analysis of insulin sensitivity in aged animals, as well as lifespan [7,8]. Most recently, we have found that existing obesity can be reversed with a specific, partial reduction of insulin production [9]. In this review, we will start by reviewing the molecular mechanisms mediating insulin action in adipose tissue, as well as insulin production and secretion, with a discussion of how these processes are imbalanced in obesity and early type 2 diabetes. We will then focus on what we have learned about obesity and insulin sensitivity by specifically and directly modulating insulin production in a variety of contexts. We will place our results in the scope of the recent broader literature and pose questions about future research and clinical opportunities for treating obesity and insulin resistance by mild suppression of insulin. We hope to address how the early normalization of insulin production and secretion can play a role in the prevention and reversal of obesity, insulin resistance, and type 2 diabetes.

Effects of Insulin on Lipid Homeostasis

Adipose tissue remodeling can theoretically occur via lipid hypertrophy and/or hyperplasia [10,11], and there is evidence that insulin has multiple direct effects on both cellular lipid metabolism [12] and adipocyte differentiation [13]. Insulin acts to inhibit lipolysis in adipocytes in

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the postprandial state [14], while promoting lipid storage through stimulating the uptake, synthesis, and storage of triglycerides in adipocytes [15]. Early experiments in rodents reveal that insulin injections into fat pads leads directly to tissue expansion due to lipid accumulation [5]. Mice with specific loss of insulin receptors in white adipose tissue have impaired adipose tissue development and are protected against diet-induced obesity, supporting the role of insulin action in adipose expansion [16–18]. Adipogenesis can be stimulated with insulin action by two mechanisms: (i) through activation of C/EBP-β and C/EBP-α transcription factors, which induce the transcription of peroxisome proliferator-activated receptor γ (PPARγ) an important regulator of adipose tissue formation, and (ii) through inhibiting FOXO1 activity, which under normal conditions negatively regulates adipogenesis [19]. Mice that lack PPARγ in adipose tissue have lean bodies and lower fasting insulin levels compared with control littermates, but this was only noted when the mice were challenged with a high-fat diet. However, due to impaired function of adipose tissue, these mice have increased lipid accumulation within their liver and muscle tissue [20]. S6 kinase 1 (S6K1) is activated by nutrients and/or insulin, leading to an increased phosphorylation of insulin receptor substrate 1 (IRS1). Mice with whole body S6K1 knockout have reduced levels of IRS1 phosphorylation and dampened insulin signaling. S6K1 knockout mice, on both chow and high-fat diets, have lower body masses due to significantly smaller adipocytes and increased lipolysis compared with control mice [21]; however generalized development of these mice appears impaired as they have leaner body masses prior to the onset of the diets [21,22]. Interestingly, loss of insulin receptors also prevents development of brown adipose tissue in mice [23]. Together, the above findings offer evidence that insulin action impacts several adipose tissue depots.

White adipose tissue can be separated into subtypes based on function, distribution, and contribution to obesity. Subcutaneous and visceral adipose tissue differ in several regards, including adipocyte type, function, lipolytic activity, vascularity, and innervation, as well as their response to insulin and other hormones [24]. Subcutaneous adipose tissue is the natural reservoir for excess energy, however when this storage area becomes overwhelmed or its ability to generate new adipocytes is impaired, lipids will accumulate in other locations, including visceral depots and organs such as the liver and pancreas. Visceral adipose tissue has been reported to be more metabolically active with enhanced sensitivity to lipolysis and appears to be more responsive to weight loss [24]. In a rodent model of type 2 diabetes, insulin treatment resulted in preferential expansion of subcutaneous adipose tissue compared with visceral tissue [25]. The mechanisms that determine fat pad expansion in humans are incompletely understood and may depend on sex, ethnicity, and age [26].

Regulation of Insulin Production and Secretion

Insulin is produced, stored, and secreted from specialized β-cells, one of at least five hormone-producing cell types that make up the complex micro-organs in the pancreatic islets of Langerhans. Insulin gene transcription and mRNA translation are primarily controlled by glucose, with the latter step considered to be the primary process under physiological control [27]. Although it had long been assumed that simply changing insulin gene expression may not result in altered circulating insulin secretion, our studies in mice show that stable but moderate changes in circulating insulin can be achieved in the long term by modulating insulin gene dosage [6,8,9]. Glucose is the primary stimulus of insulin secretion, but in some cases hormone release can also be modulated by circulating nutrients, such as amino acids and fatty acids [28]. The insulin secretory response to nutrients varies depending on life stage; newborns have relatively high plasma insulin to glucose ratios and their immature β-cells are more responsive to amino acids compared with glucose [29]. As humans and rodent models age, the level of nutrient-stimulated insulin secretion decreases *in vivo* [30,31] but not from isolated human islets

Glossary

Diazoxide: a nonselective potassium channel activator that relaxes smooth muscle by increasing membrane permeability to potassium ions. This causes voltage-gated calcium channels to close, preventing calcium influx across the sarcolemma and activation of muscle contraction. It is used as a vasodilator to treat hypertension and also inhibits insulin secretion from β-cells.
Hyperinsulinemia: excess levels of circulating insulin in relation to the level of circulating glucose. Hyperinsulinemia is a common condition linked to type 2 diabetes, however it can also arise in other conditions and diseases, such as insulinoma.
Hyperglycemia: elevated blood glucose levels. Hyperglycemia is characterized by blood glucose levels above 200 mg/dl (or 11 mmol/l) and is a hallmark sign of type 2 diabetes.
Insulinoma: pancreatic tumor that is derived from β-cells and secretes insulin. Although typically restricted to the pancreas, a small minority of these tumors can metastasize.
Lipodystrophy: a disorder in which there is an abnormal distribution of fat in the body.
Octreotide: a potent somatostatin mimetic that inhibits release of growth hormone, glucagon, and insulin. It can be used to treat growth hormone-producing tumors.

[32]. Newly synthesized insulin is preferentially secreted *in vivo* [33], however higher levels of newly synthesized insulin are secreted in response to glucose in older rats [34]. Thus, subtle but important changes in insulin production and secretion are a feature of aging.

Insulin Deregulation Early in Obesity

Chronic hyperinsulinemia, whether due to food intake or infusion, has been linked to reduced insulin sensitivity in rodent models [35,36]. Furthermore, patients diagnosed with **insulinoma** hypersecrete insulin and can develop reduced insulin sensitivity [37]. Obesity and insulin resistance are strong predictors for the onset of type 2 diabetes (Figure 1) [3], although mild insulin resistance may be protective at a very early stage of type 2 diabetes by preventing glucose overload within tissues [38]. While the relationship between insulin resistance and type 2 diabetes is well accepted and appears to be straightforward, with the concept that β-cells synthesize and hypersecrete insulin in an attempt to compensate for reduced insulin action, there are several lines of evidence that paint a more complex picture of the relationship between hyperinsulinemia and insulin sensitivity. For example, like any hormone, insulin hypersecretion can further desensitize insulin receptor responsiveness by impacting insulin receptor levels [39], as well as insulin signaling beyond the receptor [40,41]. This means that there is cell biological rationale that hyperinsulinemia is part of the problem, not just a compensatory response.

Hyperinsulinemia is a very early pathobiological event in the cascade of homeostatic defects that include obesity, insulin resistance, and type 2 diabetes [4]. For example, preclinical evidence from male C57BL/6 mice shows that insulin levels are elevated several weeks prior to the onset of obesity [6]. Similarly, hyperinsulinemia precedes insulin resistance, obesity, and enhanced lipogenesis in *Lep*$^{ob/ob}$ mice [42,43]. Finding evidence that hyperinsulinemia precedes obesity in human populations is more difficult, but evidence from some studies suggest primary elevations in insulin levels [44–46]. Interestingly, hyperinsulinemia appears to be more

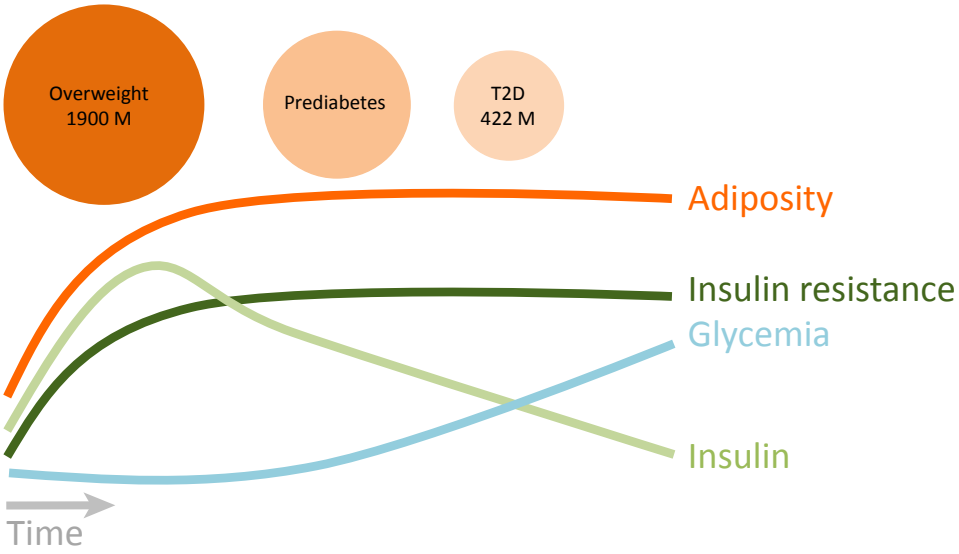

Figure 1. Insulin Deregulation in Obesity and Late-Stage Type 2 Diabetes. Increased insulin secretion occurs as a compensation mechanism for insulin resistance. Increased insulin also appears to correlate with the onset of increased adiposity. Insulin hypersecretion leads to eventual β-cell failure; without intervention this eventually results in reduced insulin secretion and, in a clinical setting, a shift from prediabetes to full-blown type 2 diabetes. Prevalence statistics from the World Health Organization (2016) [90]. Abbreviations: M, million; T2D, type 2 diabetes.

linked to increased risk of obesity in children compared with adults [44–46]. Notably, no genome-wide association signal for common obesity has yet been reported at the INS gene, pointing to the possibilities of acquired or indirect genetic action on this pathway in humans. Collectively, these studies point to acquisition of hyperinsulinemia as a primary causal factor in animal models and in some human populations.

Insulin Deregulation in Late-Stage Type 2 Diabetes

Clinically, type 2 diabetes manifests as progressive β-cell dysfunction and failure, with impairments in insulin secretion and/or functional β-cell mass in the face of insulin resistance (Figure 1) [3]. Insulin secretion is impaired in multiple ways in type 2 diabetes, including loss of the first phase of insulin secretion, loss of the normal pulsatility, and an inability to return rapidly to basal levels, which are also signs of functional immaturity (i.e., dedifferentiation). The more continuous secretion of insulin in people with type 2 diabetes could theoretically further induce insulin resistance through a desensitization process [47]. It is possible that insulin resistance of the β-cells themselves could also be involved in the pathogenesis of type 2 diabetes, since insulin has been reported to reduce its own secretion and this negative feedback loop is impaired in obese individuals [48]. The mechanisms by which systemic insulin resistance contributes to β-cell failure are not fully clear, although exhaustion caused by insulin hypersecretion is one possibility. It is also likely that glucotoxicity and lipotoxicity, and the combination thereof, contribute significantly to β-cell failure [49]. Clearly, type 2 diabetes is associated with a collection of vicious circles.

Targeting Hyperinsulinemia to Prevent and Reverse Obesity

If hyperinsulinemia is a causal factor in obesity and insulin resistance, two key early events on the path to type 2 diabetes, it should be possible to prevent or reverse these effects by early suppression of excess insulin secretion. It is important to note the distinction between fed insulin and fasting insulin levels. A variety of studies, including time-restricted feeding and intermittent fasting experiments [50,51], as well as work discussed below [6–9], point to fasting hyperinsulinemia as the more relevant target in obesity [52,53]. Fasting insulin is the product of at least three things: the physical β-cell mass, insulin production, and ability of the healthy β-cells to adequately turn off the many mechanisms that stimulate insulin release. An ideal treatment would therefore probably require specific reduction of fasting insulin.

Over the past 5 years, our group has published a series of studies investigating the effects of directly reducing insulin production on insulin secretion, β-cell mass, glucose homeostasis, insulin sensitivity, obesity, and lifespan using genetically engineered mice. We conducted these studies with the hope that they would elucidate the causal relationships between hyperinsulinemia, insulin sensitivity, and obesity, whereas previous work was limited to associations in human studies, preclinical studies, and drugs with ambiguous effects [4].

The first publication in this area compared experimental *Ins1* heterozygous male mice ($Ins1^{+/-}$:$Ins2^{-/-}$) with control littermate male mice with both copies of *Ins1* ($Ins1^{+/+}$:$Ins2^{-/-}$), fed either a moderate or a high-fat diet from weaning [6]. Control mice with both copies of *Ins1* exhibited a marked increase in fasting insulin after only 5 weeks of high-fat diet and prior to differences in body weight, whereas circulating insulin levels were markedly reduced in mice with one copy of *Ins1* at both 5 and 52 weeks of age. High-fat diet caused an expected increase in β-cell mass in control $Ins1^{+/+}$:$Ins2^{-/-}$ mice after 1 year, but this β-cell hyperplasia was prevented in $Ins1^{+/-}$:$Ins2^{-/-}$ mice with reduced insulin production [6]. This study demonstrated that diet-induced obesity could be completely abrogated, specifically preventing hyperinsulinemia in $Ins1^{+/-}$:$Ins2^{-/-}$ mice [6]. Lower body weights in the experimental mice were due to significantly smaller

fat pads, increased energy expenditure, and elevated levels of UCP1 in white adipose tissue, suggesting a brown-like adipose tissue phenotype [6]. Overall, results from male mice provide evidence that hyperinsulinemia precedes obesity, which can be prevented if insulin levels are blocked from reaching elevated levels.

In a second study, we used female mice that were null for *Ins1* to explore the role of *Ins2* in hyperinsulinemia and obesity [8]. Because *Ins1* is a rodent-specific gene, these mice could be considered genetically 'humanized'. Again, we followed experimental (*Ins1*$^{-/-}$:*Ins2*$^{+/-}$) and control littermate (*Ins1*$^{-/-}$:*Ins2*$^{+/+}$) mice for 1 year on either a moderate or high-fat diet. Here, we found that a reduction of *Ins2* gene dosage resulted in significant decreases in circulating insulin in female mice, however this was transient and by the end of 1 year, experimental mice were hypersecreting insulin. Regardless, the experimental mice were protected against diet-induced obesity with lower levels of adipose tissue, however in this experimental model we did not detect a brown-like adipose tissue phenotype [8]. A pilot study replacing *Ins2* peptide using mini osmotic pumps in experimental *Ins1*$^{-/-}$:*Ins2*$^{+/-}$ mice showed a partial reversal of the anti-obesity effect of reducing *Ins2* gene dosage [8]. An additional cohort of the experimental mice was followed for lifespan studies, which showed that a constitutive reduction in insulin gene dosage significantly extended lifespan [7]. Remarkably, old experimental mice with reduced circulating insulin were found to have significantly lower fasting glucose levels on both diets, due to an enhancement of insulin sensitivity [7]. These data provided the first *in vivo* evidence, to the best of our knowledge, that endogenous hyperinsulinemia can contribute to insulin resistance over time.

Interestingly, these studies identified apparent sex differences in the relationship between *Ins2* gene dosage and fasting insulin. Compared with circulating insulin measurements taken from the female mice [7,8], their male littermates had highly variable insulin levels that did not appear to be suppressed in mice with reduced *Ins2* gene dosage [54]. We were therefore unable to test the hypothesis that hyperinsulinemia has a causal role for obesity in this cohort of mice. Interestingly, a positive correlation between the level of circulating insulin and body mass was noted in the male mice after 1 year [54].

Work from multiple groups has also shown that indirect targeting of insulin secretion modulates body weight. For example, mice that lack mitochondrial glutamate dehydrogenase (GDH) in their β-cells display ~50% reduction of glucose-stimulated insulin secretion [55] and are completely protected against diet-induced obesity, with significantly smaller adipocytes and epididymal fat pads [56]. Another example comes from studies of G protein-coupled receptor kinase 2 (GRK2), which plays a role in glucose-stimulated insulin secretion [57]. Heterozygous GRK2 mice have reduced insulin, with a lower weight gain than control mice [57]. Together with our published studies, these data support the idea that prevention of weight gain by reducing hyperinsulinemia may be a favorable treatment for obesity and insulin resistance.

The studies described above provided direct evidence that hyperinsulinemia plays a causal role in mammalian obesity and that suppression of circulating insulin offered either transient or lifelong protection against obesity. However, the above approaches were preventative in nature and left us questioning whether insulin reduction could serve as a treatment in already obese individuals. In an attempt to address this question, we generated a mouse model in which the insulin gene dosage could be reduced using an inducible Cre-loxP system [9]. Male experimental (*Ins1*$^{-/-}$:*Ins2*$^{f/+}$:*Pdx1*Cre^{ERT}) and control littermate (*Ins1*$^{-/-}$:*Ins2*$^{f/+}$) mice were placed on a high-fat diet for 12 weeks to stimulate hyperinsulinemia and obesity [9]. Remarkably, we found that partial reduction of insulin in adult experimental mice caused a significant 5% weight loss within 5 weeks of tamoxifen treatment, with specific reductions in gonadal and perirenal

adipose depots, and reductions in Ptrf/Cavin protein levels in gonadal adipose tissue [9]. Ptrf/Cavin is a human **lipodystrophy** gene that is nutritionally related [58] and plays roles in adipocyte differentiation, expandability, and lipid uptake [59]. These results demonstrate that adiposity, and by extension obesity, can be controlled by moderate changes in circulating insulin. Circulating insulin levels were variable, however we noted an almost complete recombination using a reporter, and islet *Ins2* mRNA expression as well as insulin content was significantly reduced in these experimental mice [9]. Taken together, the evidence from these experimental approaches, in which insulin is directly suppressed, offer support for the theory that hyperinsulinemia can play a causal role in mammalian obesity. This mechanism appears to be conserved evolutionarily, since reducing the expression of insulin-like peptide in *Drosophila* likewise prevents diet-induced fat accumulation [60].

Weight Loss with Reduced Hyperinsulinemia is Dependent on the Maintenance of Glucose Homeostasis

Over the course of our studies designed to test the effects of reduced insulin production on body weight, we paid close attention to glucose homeostasis. In the first study, where insulin production was reduced the most dramatically, $Ins1^{+/-}$:$Ins2^{-/-}$ had impaired glucose homeostasis relative to $Ins1^{+/+}$:$Ins2^{-/-}$ controls early in life that rectified in the majority of animals [6]. The more moderate reduction of insulin production observed in $Ins1^{-/-}$:$Ins2^{+/-}$ mice relative to controls led to improved normal glucose tolerance throughout adult life, and, in fact, lower fasting glucose and improved insulin sensitivity in old age [7,8]. These studies demonstrated that the anti-obesity effects of targeting hyperinsulinemia occurred in the absence of sustained impairment of glucose homeostasis. However, in our study using leptin-deficient *ob/ob* mice, constitutive loss of two or three insulin genes attenuated weight gain by 50–90% compared with *ob/ob* mice with three of the four insulin alleles intact, whereas the more substantial reduction in circulating insulin levels by 75–95% resulted in fasting **hyperglycemia** by 4 weeks of age and progression to diabetes [43]. This result indicated the importance of maintaining glucose homeostasis to achieve the benefits of reduced insulin. Recently, we have found that the anti-obesity effects of moderately reducing excess insulin are dependent on the maintenance of normoglycemia using our inducible model. While the majority of cohorts we have studied exhibited only moderate insulin suppression, accompanied by weight loss and normoglycemia [9], we did observe a cohort in a pilot study where insulin levels were decreased to the point that fasting glucose rose above an average of 16 mM and it is notable that this group of mice did not respond with a weight-loss benefit. We interpret these observations as suggesting that intact glucose homeostasis is required for the beneficial effects of reducing hyperinsulinemia in the context of obesity. This would mean that any future intervention designed to reduce excess insulin should be provided to obese patients prior to the onset of frank diabetes (Figure 2).

Pharmacological Correction of Hyperinsulinemia in Preclinical Models and Clinical Trials

Experimental and clinical studies provide evidence that hyperinsulinemia precedes obesity (Table 1) [4] and that insulin response can also dictate weight gain [61]. It is challenging to properly test in a clinical setting whether reducing insulin levels has anti-obesity effects, especially with the limited pharmacopeia capable of safely inducing a moderate reduction in basal insulin secretion. However, pharmacologically, insulin hypersecretion can be suppressed with treatment of the somatostatin analogue **octreotide** [62] or the nonselective potassium channel opener **diazoxide**, which inhibits membrane depolarization [63], although clearly one would expect a narrow dose-range where anti-obesity actions are evident without deleterious effects on glucose homeostasis. In a series of studies conducted on obese Zucker rats, diazoxide reduced weight gain [64,65]. Clinical trials based on diazoxide treatment were

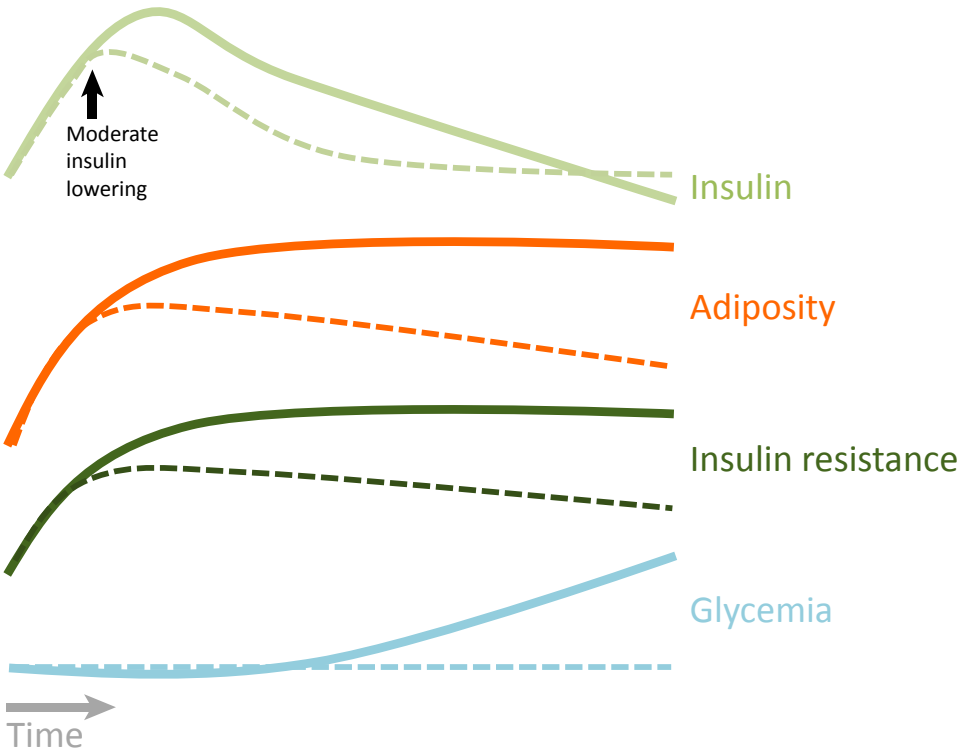

Figure 2. Reducing Circulating Insulin Levels Can Protect and Reverse Adiposity, Insulin Resistance, and Hyperglycemia. Moderate lowering of insulin levels early in the onset of increased insulin secretion (black arrow) effectively reduces adiposity, insulin resistance, and hyperglycemia.

less clear. For example, diazoxide treatment (200 mg/day for 8 weeks) had anti-obesity effects in a study of hyperinsulinemic individuals who were reported to have significantly reduced postprandial insulin secretion [66] but had no effect in a study where a difference in postprandial insulin could not be measured [67]. Obesity in children with hypothalamic-pituitary lesions was not reduced with a twice-daily dose of 4 mg/kg of diazoxide [68]. Anti-obesity effects have been reported in men following mild caloric restriction, increased physical activity, and 900 mg/day diazoxide treatment [69]. One likely reason for the different outcomes in these studies is the level of diazoxide dose. Although octreotide treatment in obese individuals successfully reduced weight in two clinical trials [70,71], individuals with the greatest degree of insulin secretion benefited the most [70]. Studies with diazoxide and octreotide should not be interpreted as strong evidence for a primary role of insulin hypersecretion in obesity, as both can directly impact other organs that are also implicated in weight regulation, including white adipose tissue and the hypothalamus [64,72,73]. Moreover, diazoxide may have additional off-target effects that complicate the interpretation of these data.

Nonpharmacological Approaches to Moderate Insulin Suppression

There are many possible dietary interventions that could be used to lower insulin, including diets low in carbohydrates, intermittent fasting and time-restricted feeding, and even simple caloric restriction, whether via dietary modification or bariatric surgery [74–77]. Indeed, there are growing and competing literatures supporting a plethora of insulin-lowing interventions. Although basal insulin levels in healthy humans and experimental animals are widely variable

Table 1. Evidence For and Against Hyperinsulinemia Associating with and/or Causing Various Disease States[a]

Disease state	Human/primate evidence for association, Refs	Preclinical evidence for causality, Refs	Loss-of-function clinical evidence for causality, Refs	Preclinical or clinical evidence against causality, Refs
Obesity	[91–93]	[6–9,65]	[66,69–71]	[67,68]
Insulin resistance	[52,91]	[42,94,95]	[96]	
Type 2 diabetes	[4,53,92,93]			
NAFLD/NASH	[97,98]	[6,7]		
Accelerated aging	[93,99]	[7]		
Inflammation	[100]	[3,6,9,101]		
Hypertension	[102–104]			
PCOS	[105,106]			
Cancer	[93,107]	[108]		

[a]Abbreviations: NAFLD/NASH, nonalcoholic fatty liver disease/nonalcoholic steatohepatitis; PCOS, polycystic ovarian syndrome.

Outstanding Questions

What are the molecular mechanisms by which a modest reduction in circulating insulin improves insulin sensitivity and obesity?

Can excess insulin be lowered clinically without deleterious effects on glucose homeostasis?

What are the ideal pharmacological or nonpharmacological methods to lower excess insulin clinically?

How will clinicians know when insulin is no longer in excess?

[54,78], evidence suggests that obese individuals who secrete higher levels of insulin respond best to diets which lower postprandial glycemia and insulinemia, whereas obese individuals with lower insulin secretion levels respond best to low-fat diet intervention [79,80]. Interestingly, patients exhibiting hyperinsulinemia following weight loss are more likely to regain weight [81]. Weight loss was greatest in nondiabetic patients following a 2 year randomized trial on a low-carbohydrate diet, next followed by a Mediterranean diet and a low fat diet [82]. Restricting fructose intake is another successful dietary intervention in obese children that lowers hyperinsulinemia [83,84]. Although less clear in regards to an effect on obesity, evidence suggests a positive correlation between low sugar intake and reduced fasting insulin levels in humans [85]. Thus, there are many possible dietary approaches that are known to lower insulin and that may have positive effects on obesity and insulin sensitivity. We eagerly await ongoing studies in this active area of investigation and hope that more nutritional studies will include measurements of insulin.

Concluding Remarks and Future Perspectives

We have presented numerous experimental and clinical studies that provide evidence for a causal role of hyperinsulinemia in the progression of obesity. Reducing hyperinsulinemia can be accomplished with pharmacological, dietary, and physical intervention; however it is clear from both experimental and clinical trials that insulin level and obesity is extremely variable and in normalizing both it appears that we need to focus on the individual [75]. Although gene therapy is gaining traction in experimental models and preclinical trials, we are still far from human clinical trials [86,87]. Therefore, we need further powerful experimental studies accompanied by well-defined large clinical trials that focus on personalizing nutritional, physical interventions and behavioral modifications [88,89] to maintain insulin levels within a healthy range (see Outstanding Questions).

The preclinical data discussed in this review provides the biological rationale for early and moderate lowering of glucose levels to prevent and treat obesity/insulin resistance, which, as long as it does not impair glucose homeostasis, would be predicted to eventually reduce the number of individuals transitioning to late-stage type 2 diabetes (i.e., insulin deficiency). At this time, it is unclear exactly what a mild clinical insulin-lowering treatment might look like. Several options are theoretically possible, including more advanced, specific, and titratable analogues

of diazoxide or octreotide. However, any treatment should be temporary, to save endogenous insulin secretion in individuals who might fail at such a therapy.

Disclaimer Statement

The authors have no conflict of interest to disclose in relation to this work.

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