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Insulin Resistance: Have we missed the real cause by continuing to focus on the post receptor defects?

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ABSTRACT

Insulin resistance (IR) is a serious condition that precedes Type 2 Diabetes (T2D) and obesity. Despite extensive knowledge of insulin receptors and their function nearly 50 years of research has failed to define the post receptor binding defects in signalling responsible for IR. The concept of cellular spare receptors diverted attention from the effect of hyperinsulinemia to cause receptor changes. Hyperinsulinemia, an inevitable accompaniment of insulin resistance (except in starvation) reduced the number and affinity of available receptors, and increased the need for higher insulin concentrations to produce a response. In addition, current therapies for IR include insulin and sulphonylurea that reduced blood glucose but increased pancreatic secretion of insulin, and weight gain. Insulin sensitizers such as thiazolidines, metformin, diet, exercise, GLP-1 receptor agonists and SGLT2 inhibitors improve IR first by causing weight loss, appetite suppression and thereby lowering blood glucose and may or may not facilitate a reduction in insulin. Continual therapy is required to prevent weight gain and the remission of IR. Recent reports have indicated that calcium supplements in insulin resistant patients can alleviate insulin resistance without increasing insulin concentrations, but this requires further confirmation. This effect was supported by the early reports on receptor binding that showed calcium at non physiological concentrations increased receptor affinity and lowered the threshold for insulin action.

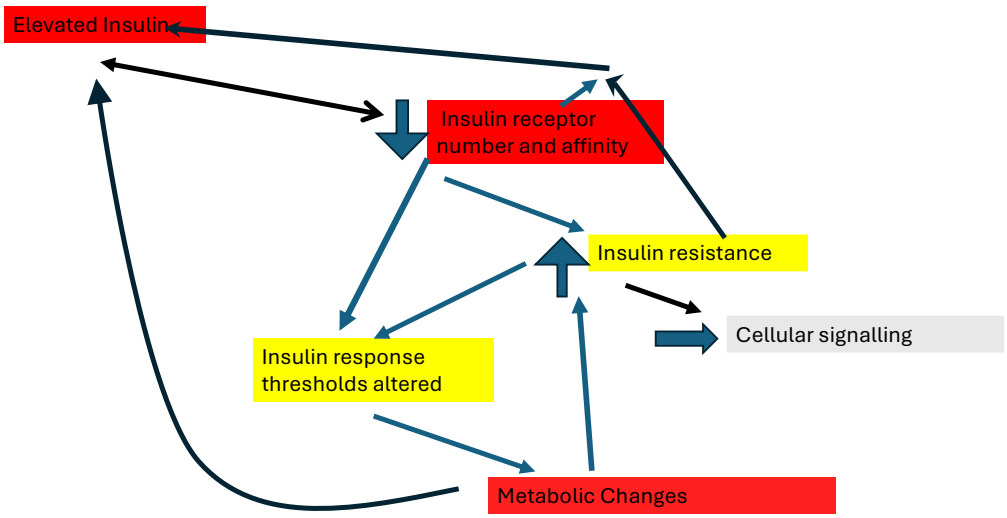
Using the fat fed mouse model we have shown that commencing an exercise program together with a high fat diet (HFD) prevented the onset of hyperinsulinemia and insulin resistance without causing a decrease in food intake. Completely opposite effects were seen where 6 or 12 weeks of HFD diet preceded the exercise. Here the high degree of insulin resistance was unaltered by exercise. Since insulin signalling defects have been difficult to find, it appears that the initiating factor for IR may be the insulin induced changes in receptor number and affinity. IR and sulphonylurea can be responsible for pancreatic exhaustion but the decrease in available insulin does not correct the secondary alterations in whole body metabolism that result in T2D and obesity.

Introduction

Insulin resistance (IR)[1] is a serious condition that generally leads to obesity, Type 2 Diabetes (T2D) and hyperinsulinemia which are inextricably linked together[2-4]. Chronic insulin administration to humans also induces IR and leads to obesity as do the genetic and pharmacological interventions that cause hyperinsulinemia and IR[5]. IR can be detected in first degree relatives of T2D patients and has been reported in cross-sectional studies of the population where it has a predictive capacity for the onset of disease. While the ability of a ligand to desensitise a target tissue is well recognised [2], there are exceptions in starvation and normal pregnancy. The IR exceptions (normal pregnancy and starvation) appear to use IR as a safety mechanism to preserve glucose for the foetus and the brain. However, despite the process whereby insulin itself induces IR signalling defects have remained a major focus of attention [2] and IR is still poorly understood.

Therapeutic interventions that increased insulin reduced blood glucose but perpetuated the hyperinsulinemia further compounding the IR and leading into pancreatic exhaustion (e.g. sulphonylurea failure) predisposing those subjects to diabetes or obesity [6]. Again illustrating the importance of high insulin concentrations in initiating and maintaining the IR. There is a general consensus that chronic caloric overload in the population is a major contributor to the onset of IR [3,7,8], and initiates the increased insulin concentration required to lower blood glucose. While IR may be a protective mechanism in some cases (normal pregnancy and starvation) it fails to protect the body from the consequences of excess metabolites, allowing the glycation of proteins, increasing fat cell proliferation and fat cell deposition in inappropriate places.

Figure 1:



The storage problem

In an evolutionary sense intracellular storage was essential to cope with the feast and famine usually experienced by early and primitive humans (e.g. the Khoikhoi or San). In this way limiting the damage done by high circulating metabolites (e.g. glycation). Glucose stored as glycogen in muscle, liver and fat, is inefficient and bulky, requiring an equivalent amount of water and glycogen to be stored. It was much more efficient to store triglycerides in specialised droplets in fat cells. To store the excess nutrient either an increase in capacity of the cells or an increase in fat cell number was required. In single cell and simple multicell organisms the presence of nutrient would signal the cells to grow and to proliferate ensuring survival. In multicellular organisms uncontrolled proliferation would be damaging to organ and tissue structure/organisation. A side effect of the hyperinsulinemia that lowered blood glucose, was that it increased fat cell proliferation. Separating nutrient storage from growth and proliferation in multi-organed species is important, and may explain why we have both insulin and Insulin like Growth Factor (IGF). Two highly related hormones with similar receptors. A further limit to uncontrolled proliferation were the IGF binding proteins that control the accessibility of IGF's to tissues. However, in IR, hyperinsulinemia, nutrient overload and storage problems result in proliferation of fat cells and whether they are situated in either subcutaneous or visceral locations has important implications for body health. When the body's capacity to store lipid becomes saturated and coupled with the increased lipolysis and stimulated lipogenesis from IR, lipids will be stored in inappropriate tissues such as liver, muscle and around organs[5,9]. Since IR has reduced the recruitment of GLUT-4 [5]and CD36 [10]in insulin sensitive tissues it limits the uptake of glucose and fatty acids to form triglycerides in most tissues except the liver, where triglycerides are able be stored, causing fatty liver.

Insulin resistance and the insulin Signalling

With the early discovery of the insulin receptor (1970's) and later the elucidation of its signalling pathways (1980's), we had hoped that an understanding of the many and complex parts of the role for insulin in the

control of metabolism would result. However early investigation revealed the presence of abundant insulin receptor proteins on the cell surface and there were "spare insulin receptors" available to initiate an insulin response. The presence of spare receptors, meant that because increasing insulin concentrations produced a response it directed research to attribute the IR to a malfunctioning intracellular insulin signalling system. This idea pursued despite the earlier evidence that insulin receptor numbers were directly controlled by circulating insulin [11] and insulin sensitivity was altered by changes in receptor number and receptor affinity[1,11,12] as well as by the post receptor signalling defects. However, it must be pointed out that despite over 40-50 years of investigation a definitive mechanism or defect in the post receptor signalling network has not been elucidated[5,9]. Indicating that we need to look for an initiating factor earlier in the process such as the reduction in receptor numbers and affinity by insulin[8].

Is insulin resistance a result of post receptor signalling changes?

Hyperinsulinemia is a major controller of insulin receptor numbers on the cell surface and of insulin receptor affinity both of which are major factors that can produce either a reduction in maximal response or a rightward shift in the dose response curve for insulin action[1,12,13]. As there were spare insulin receptors it was logical to assume that there were also spare receptor signalling components and recent reviews have confirmed this. They showed that the capacity of the IRS, PI3K and AKT2 signalling pathways were not a limiting factor in IR and even established that "homozygous deletion" of AKT2 decreased AKT phosphorylation events by 90% but had no effect on insulin stimulated AKT substrate phosphorylation, glucose uptake and protein synthesis [5,9]. IRS knockouts develop insulin resistance but do not develop diabetes [14].

What are the thresholds for insulin responses?

Insulin responses have thresholds, for instance inhibition of lipolysis occurs in fat cells at low insulin concentrations, (78 pmol/L) but lipogenesis, the suppression of gluconeo-genesis and hepatic glucose output were unaffected at these concentrations [15]. It required 6 times the concentration to lower glucose or inhibit lipogenesis (454 pmol/L)[15]. The "negative cooperativity" shown by the insulin receptor[16] can offer an explanation as negative cooperativity theory strongly supports the presence of thresholds in metabolic responses to stimuli[17]. As receptor occupancy increases the affinity decreases and insulin dissociates from the receptor [16] and increases internalisation of receptors. The insulin induced reduction in receptors (number and affinity) would require higher insulin concentrations to elicit a response, leading to an hyperinsulinemic IR state. The insulin receptor dimer is bivalent and binds between 1 and 4 insulin molecules, with the first insulin bound crosslinking one end of insulin to one alpha subunit of the receptor dimer and the other end of the insulin molecule crosslinking to the complimentary sites on the other alpha subunit of the insulin receptor dimer [18]. A second insulin binds with lower affinity to the vacant complimentary sites of the same receptor protein dimer completing an X like configuration [18,19]. Even higher receptor occupancy is required for proliferative responses [18].

Can insulin induced receptor changes in number and affinity trigger IR?

The evaluation of insulin receptor affinity changes requires full insulin dose response curves usually as Scatchard plots, a time consuming and detailed procedure. It has become more customary to estimate the concentration of insulin bound that produces a half maximal response (the ED50) which obscures the decreased high affinity binding sites and only reflects the average affinity of the sites. The first insulin binds with a high affinity and lowers the affinity for the 2nd, 3rd and 4th insulin molecules bound by the other binding sites of the receptor dimers. Binding of insulin to complimentary sites on the receptor dimer, causes a conformational change to the beta subunits and allows autophosphorylation to start the insulin signalling process [18]. Some insulin responses may be triggered by occupancy of the high affinity sites (e.g. inhibition of Lipolysis) and the occupancy of the 2nd, 3rd and 4th sites may be required to activate insulin responses such as glucose uptake, inhibition of gluconeogenesis and full occupancy could be required to stimulate cellular proliferation. All of these insulin thresholds could be exceeded in the IR state.

How to cope with excess nutrition?

The problem of combating the nutrient excess, in the presence of hyperinsulinemia and IR, has been addressed using both pharmacological and life style interventions [20,21]. Exercise has been a prominent intervention, and caloric restriction with or without very low calorie diets has often been recommended for the treatment of obesity and to limit the progression of IR to T2D [20]. The pharmacological interventions for the treatment of Diabetes/obesity include insulin injections, metformin, thiazolidinediones, glucagon like peptide receptor agonists, sodium glucose transporter inhibitors, meglitinides, glucagon like peptide receptor agonists (GLP-I RAs) and sulfonylureas. The American Diabetes Association Professional Practice Committee 2024 recommends metformin, thiazolidinediones (TZD), glucagon receptor agonists (GLP-I RAs), and sodium glucose transporter inhibitors (SGLT2 inhibitors). Metformin and GLP-I RAs have an ability to decrease weight and address the insulin sensitivity problem usually by appetite suppression and increased glucose handling but upon cessation of therapy IR soon re-exerts itself. TZD's produce small weight loss and are associated with lipotoxicity and the TZD PPAR agonists increase fat cell hyperplasia [22]. GLP-1 RAs act by suppressing weight gain and do not supress but enhance insulin secretion by the pancreas [23] and therefore increase or maintain hyperinsulinemia [20]. SGLT2 inhibitors address a physiological mechanism to prevent the adverse effects of high blood glucose in increasing the ability of the kidney to excrete glucose lowering the threshold for the kidney to reabsorb glucose from the kidney tubules [20]. With the exception of the GLP-1 RAs it is a constant observation that most pharmacological interventions have a limited potential to reduce IR and long term weight gain

but weight usually returns within 12 to 18 months, prompting many to resort to gastric restriction surgery, as a more permanent solution. However the new varieties of GLP-1 RAs are very effective in reducing weight and may replace gastric restriction surgery, but the effect of GLP-1 RAs to enhance pancreatic insulin secretion[23] and not to correct the hyperinsulinemia but still have a profound effect on weight loss is still under investigation. By enhancing insulin secretion they are leaving the initial stimulus for IR intact. The continued presence of hyperinsulinemia means that IR remains and is a self perpetuating phenomena. The early suppression of the hyperinsulinemia may be the only way to correct this damaging cycle. Early intervention would be important because the reduction in insulin secretion after pancreatic exhaustion does not change the course of IR.

Using the high fat fed mouse model, we instituted an exercise program after IR and weight gain were established and observed minor effects on insulin concentrations, energy use, small changes in UCP-1 and in decreased storage of lipid over the 16 week period of observation. We also observed that different types of isocaloric exercise had different effects on the metabolic profile. What was more significant was when we instituted an exercise program at the start of the high fat diet [24] it prevented IR and hyperinsulinemia. In this high fat diet model both high intensity exercise and endurance prevented increased body weight, increased lean mass, and improved insulin sensitivity by 22%, decreasing adipose hyperplasia and inflammation[24]. It is obviously hard to predict when to start an exercise program in the period preceding caloric overload and this does not seem a practical solution other than to recommend a healthy lifestyle change that is sustained and commenced early in life.

Inflammation is typically present in the IR state and IR has been produced by inducing endoplasmic reticulum stress [25,26]. When an inflammatory stimulus was used to induce IR, post receptor insulin signalling was unaltered and did not contribute to the IR. Suggesting that multiple metabolic changes that are induced by either hyperinsulinemia or chronic inflammation may make it difficult to be able to reverse the progression of IR to obesity and type 2 diabetes once set in train. The initial event in IR may be reduced receptor affinity and receptor numbers which then results in many metabolic disturbances that can trigger inflammatory processes and other metabolite induced changes in insulin action compounding the IR.

Where do we stand in combating IR?

Exercise has a dramatic effect on receptor affinity in both mice and man [13,27]. Exercise is also a strong stimuli for glucose and lipid uptake [28,29], independent of insulin action. By lowering glucose, exercise reduces the need for insulin secretion, hence it can prevent the hyperinsulinemia seen in IR. The concept of increased GLUT 4 in relieving IR was addressed by the James group [5]. However, whether exercise can sustain the effect in the presence of caloric excess and maintain low blood glucose after its effect on glucose transporters has declined has not been answered. It would seem that exercise would need to be accompanied by strict dietary control in order to be able to mimic the effects seen in our study where exercise began at the time of high fat feeding [24]. The new GLP-1 RA's reduce weight significantly but in not reducing insulin secretion[23] they are all not able to reduce IR [30]. Their mechanism of action seems to be more dependent upon weight loss than on the changes in receptor sensitivity that are seen with diet and exercise. They all reduce post-prandial glucose insulin and C-peptide after 2 -4 weeks of treatment, but other indexes of insulin resistance in either liver or peripheral insulin tissue were still present [30]. Recent reports have indicated that calcium supplements for insulin resistant patients can alleviate insulin resistance without increasing insulin concentrations but it requires further confirmation [31-35]. This effect was supported by the early reports on receptor binding showing that at non physiological concentrations of calcium and other divalent cations the increased receptor affinity facilitated insulin action at lower concentrations[36].

Conclusion

Treatment of IR remains a significant problem with the main frontline defences being diet and exercise but there are hopes that longer term studies of the GLP-1 RA's may provide a solution. Early reduction or removal of the stimuli that produces hyperinsulinemia may be the only way to tame the self perpetuating process that reduced insulin receptor number and affinity and halted this vicious cycle. Controlling this process early in IR may prevent the compounding effect of impaired insulin action on the secondary metabolic changes responsible for T2D and obesity. Late intervention would be unlikely to succeed as pancreatic failure reduces insulin but does not correct the IR. Appetite suppression, diet, exercise along with the GLP-1 RA's leaves us with a good process to maintain remission but we still have a poor prognosis for the future cure or prevention of IR and its progression to obesity and Type 2 diabetes.

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