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Myocardial Insulin Resistance: An Overview of Its Causes, Effects, and Potential Therapy

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1. Introduction

Normal insulin sensitivity is essential for the maintenance of normal circulating carbohydrate and lipid levels and their metabolism. In healthy individuals elevated blood glucose levels stimulate the pancreas to release insulin which lowers blood glucose levels by stimulating glucose uptake and metabolism in muscle, adipose tissue and several other insulin sensitive organs. Blood glucose increases are not only countered by increased tissue glucose uptake but also by insulin induced suppression of hepatic glycogenolysis and gluconeogenesis. Besides its effects on blood glucose, insulin also affects circulating lipid levels by reducing hepatic very low density lipoprotein cholesterol (VLDL-cholesterol) formation from free fatty acids (FFAs). This is primarily due to the reduced free fatty acid supply to the liver caused by insulin induced suppression of lipogenesis in adipose tissue [1]. In addition to its effects on lipogenesis, insulin also reduces lipolysis in adipose tissue by inhibiting hormone sensitive lipase. The latter hydrolyses adipocyte triglycerides to release free fatty acids and glycerol into the circulation. When delivered acutely, insulin inhibits fatty acid synthase while chronic hyperinsulinaemia (as occurs in insulin resistance) may induce fatty acid synthase activity and increase fatty acid synthesis [2]. The net effect of elevated insulin in normal healthy individuals is to reduce circulating glucose and free fatty acid levels.

When an individual becomes insulin resistant, control of circulating lipid and blood glucose levels is compromised. Insulin resistance ensues when normal physiological concentrations of insulin are unable to induce effective uptake of glucose by insulin sensitive tissue. As a compensatory mechanism aimed at maintaining euglycaemia, pancreatic insulin secretion increases leading to a state of hyperinsulinaemia. If the elevated insulin levels are inadequate to fully compensate for the insulin insensitivity glucose intolerance ensues. The degree of glucose intolerance in insulin resistant individuals is thus dependent on the extent

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of the loss of the *in vivo* function of insulin, and the ability of the pancreas to adjust for this by secreting more insulin [3, 4]. Once elevated circulating levels of insulin are no longer able to maintain euglycaemia, and glucose levels deviate beyond normal physiological ranges an individual is considered to be frankly diabetic.

Myocardial insulin resistance translates to compromised intracellular insulin signalling and reduced glucose oxidation rates in animal models of obesity [5] and adversely affects myocardial mechanical function and tolerance to ischaemia and reperfusion. In this chapter we will review the mechanisms implicated in the aetiology of insulin resistance (skeletal and heart muscle) and discuss the effects of insulin resistance on cardiac metabolism, mechanical function and tolerance to ischaemia and reperfusion. We will also briefly review therapies used to prevent or counter insulin resistance and its associated adverse effects on the cardiovascular system.

2. Myocardial insulin signalling

Insulin induced activation of the insulin receptor (IR) invokes a cascade of events which ultimately enhances myocardial glucose uptake and metabolism. Insulin binding to its receptor results in autophosphorylation and activation of the insulin receptors (IRs) intrinsic tyrosine kinases. Following phosphorylation the insulin receptor phosphorylates insulin receptor substrate (IRS) [6] which subsequently associates with phosphoinositide 3-kinase (PI3K) via its p85 subunit [7, 8]. These events are vital for initiating insulin's effects on glucose metabolism [6, 9, 10]. Activated PI3K will induce (via various signalling mechanisms) protein kinase B (PKB/Akt)[11] which plays a pivotal role in glucose metabolism by regulating the translocation of the cytosolic glucose transporter type 4 (GLUT4), to the sarcolemma [12, 13]. Inhibition of PI3K and/or PKB/Akt attenuates sarcolemmal GLUT4 translocation, effectively reducing insulin stimulated signalling and glucose uptake [14, 15]. Besides facilitating glucose uptake via GLUT4, insulin stimulation also increases glycolytic flux rates through activation of phosphofructosekinase 2 (PFK-2) which promotes the production of fructose-2,6-bisphosphate from fructose-6-phosphate [16-18]. Fructose-2,6-bisphosphate stimulates PFK-1 activity, which will also enhance glycolysis (see review by Hue *et al*. [18]).

Although insulin increases long chain fatty acid (LCFA) uptake into the cardiomyocyte by increasing sarcolemmal fatty acid translocase/cluster of differentiation 36 (FAT/CD36) [19], elevated insulin levels also suppress tissue fatty acid β-oxidation rates. This suppression is most likely due to the effects of by-products of elevated glucose oxidation on malonyl-CoA levels [20]. As acetyl-CoA levels increase, acetyl-CoA carboxylase (ACC) is activated which increases malonyl-CoA induced inhibition of fatty acid oxidation.

3. The role of obesity or a high fructose diet in the aetiology of insulin resistance

Insulin resistance is strongly associated with both obesity and the consumption of high fructose containing diets [21-25]. Although not all obese individual are insulin resistant,

there is a strong association between obesity and insulin resistance [21, 25]. Adipose tissue is not only a storage organ but also a metabolically active organ synthesising and secreting a large range of substances that include fatty acids, pro-inflammatory cytokines, angiotensin II, leptin, resistin, visfatin and other adipocytokines [26] that can all influence tissue metabolism. Obesity and high fructose diets both induce increases in: 1) circulating FFAs [27, 28], 2) renin-angiotensin system (RAS) activity [29, 30], and 3) inflammation (caused by tissue and macrophage derived pro-inflammatory cytokines) [31] that are all associated with, and implicated in insulin resistance.
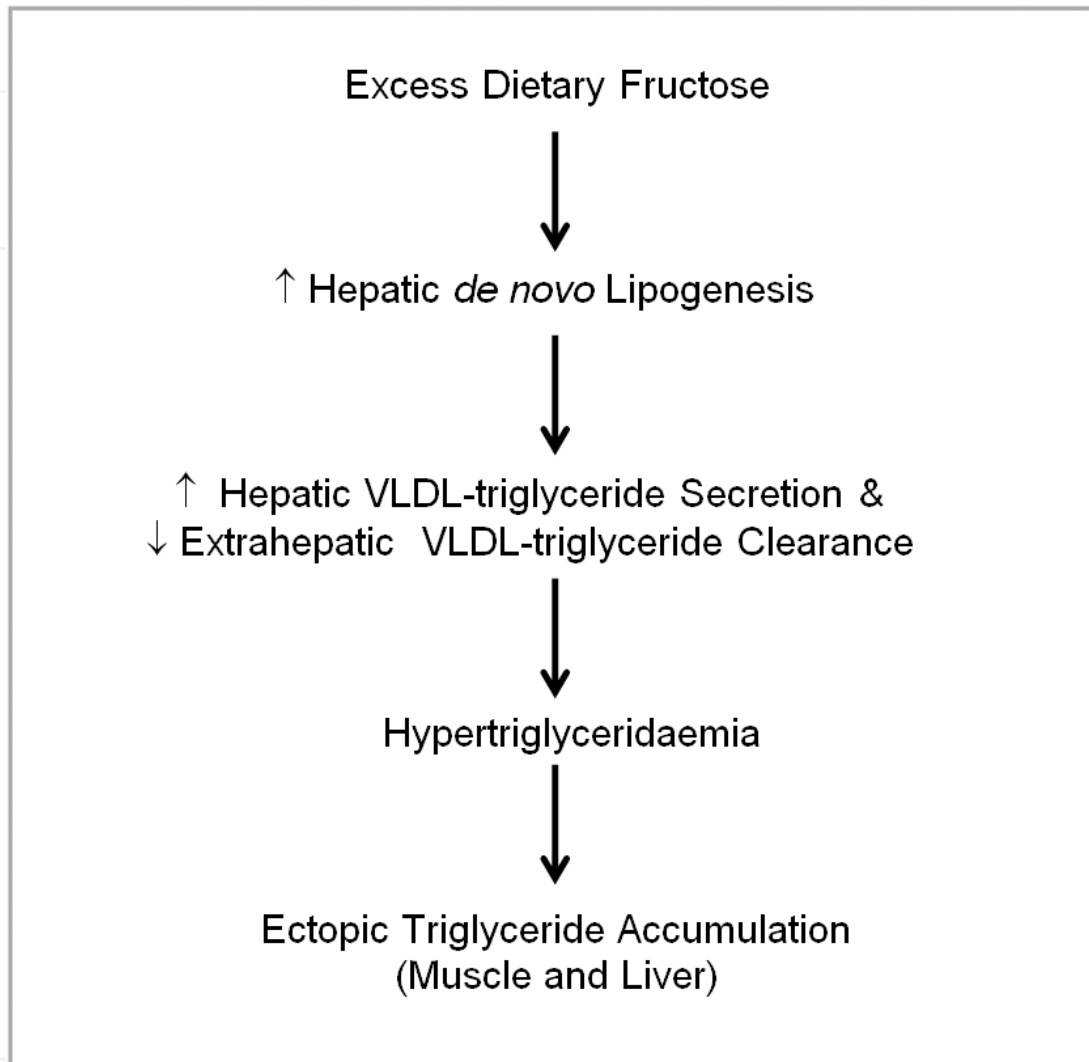
Besides the negative impact of obesity on circulating lipids, recent studies provide convincing evidence for a role for high fructose diets in dyslipidaemia and insulin resistance [24, 27, 32]. These lipid profile altering effects of high fructose diets are primarily caused by fructose induced alterations in hepatic lipid metabolism [22-24]. Hepatic fructose metabolism differs significantly from glucose metabolism with fructose being a lipogenic sugar that promotes the deposition of triglycerides in adipose tissue and ectopic organs such as the liver and muscle. This tissue triglyceride accumulation eventually contributes to dyslipidaemia and insulin resistance [22, 27, 33].

Increasing dietary fructose consumption increases plasma triglyceride levels through stimulation of hepatic lipogenesis [34] and decreased VLDL-triglyceride removal from the plasma by adipose tissue [35]. Fructose evidently also activates genes involved in hepatic *de novo* lipogenesis [36, 37] which causes increased hepatic fatty acid generation. These fatty acids are incorporated into hepatic triglycerides which promotes VLDL-triglyceride synthesis and release from the liver (Figure 1)[38].

A recent review highlights the possible effects of high fructose diets on hepatic insulin resistance [22]. These authors propose that high fructose diets promote hepatic inflammation by increasing fatty acid β-oxidation (secondary to hepatic lipid accumulation) which generates peroxidation products that stimulate inhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ) and activate nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB). The NFκB then enters the nucleus and induces the transcription of genes that encode for pro-inflammatory cytokines that include tumour necrosis factor alpha (TNFα) and interleukin-6 (IL-6). These cytokines potentially activate c-Jun N-terminal kinase-1 (JNK-1) which will increase inhibitory serine[307] phosphorylation of IRS-1 and contribute to hepatic insulin resistance [22] (Figure 2).

Because of its lipogenic effects, fructose causes more marked changes in 24 hour lipid profiles than does the consumption of glucose while also favouring visceral rather than subcutaneous fat deposition [33]. This fat deposition pattern differs from that of glucose which promotes subcutaneous adipose tissue deposition rather that visceral fat deposition in men [39]. In rodents, a high fructose diet increases intrahepatic fat content and serum VLDL-triglyceride concentrations within 6 weeks of feeding. In the same study intramuscular fat content was increased within 3 months of initiating the high fructose feeding with these changes being closely followed by hepatic and muscle insulin resistance [32]. Another animal based study supports a role for high fructose diets in increased hepatic VLDL-triglyceride

secretion [40]. In humans increasing fructose content in the diet increases plasma triglycerides [34, 41], decreases VLDL-triglyceride clearance [35] and increases triglyceride deposition in hepatocytes and skeletal muscle within a week of increasing dietary fructose content [41].

Excess Dietary Fructose

↓

↑ Hepatic *de novo* Lipogenesis

↓

↑ Hepatic VLDL-triglyceride Secretion &
↓ Extrahepatic VLDL-triglyceride Clearance

↓

Hypertriglyceridaemia

↓

Ectopic Triglyceride Accumulation
(Muscle and Liver)

Figure 1. Mechanism for high fructose diet induced dyslipidaemia and ectopic lipid accumulation. High fructose diets promote hepatic *de novo* lipogenesis and lipid accumulation and reduce extra-hepatic VLDL-triglyceride clearance. The associated hypertriglyceridaemia promotes adipose tissue expansion (obesity) and muscle lipid accumulation which induces insulin resistance.

Since high fructose diets are often also associated with obesity, it is difficult to differentiate between the effects of the changes in dietary fructose content and the effects of obesity on tissue insulin sensitivity. Data from studies demonstrating that some individuals are obese but metabolically healthy [42] and metabolic syndrome appears to be more closely linked to intrahepatic fat content than obesity *per se* [1, 41, 43], suggests that hepatic lipid metabolism and circulating lipid levels play a critical role in the induction of insulin resistance in response to obesity and high fructose diets. Tappy and co-workers [23, 24] recently proposed that fructose increases hepatic *de novo* lipogenesis which leads to intrahepatic lipid deposition, hepatic insulin resistance and increased VLDL-triglyceride secretion. This

potentially leads to increased visceral fat deposition while the elevated VLDL-triglyceride and inhibition of lipid oxidation (induced by fructose) may promote ectopic fat deposition in muscle with lipotoxicity leading to systemic insulin resistance (Figure 1) [22-24]
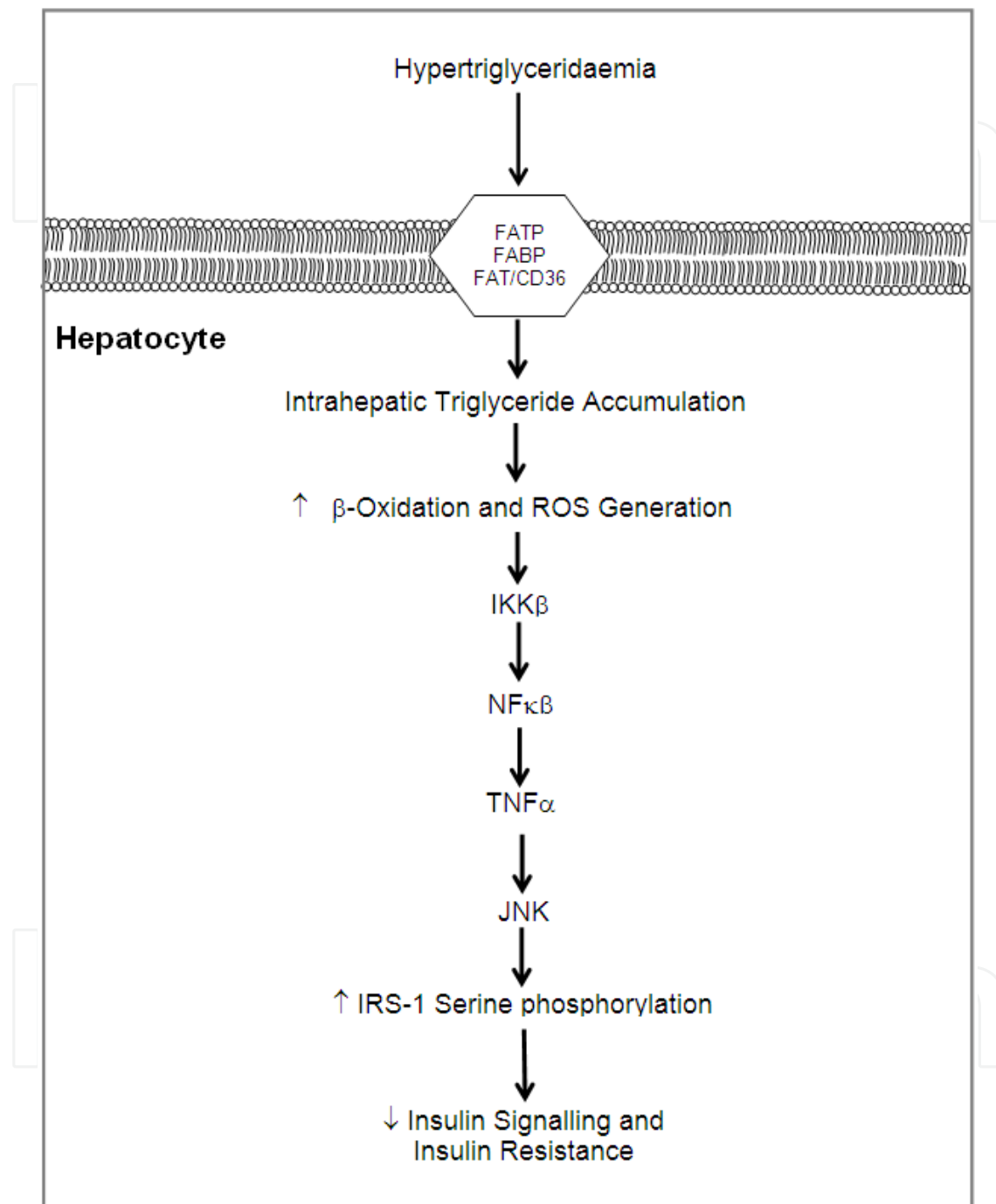
Figure 2. The proposed mechanism for intrahepatic lipid accumulation induced stimulation of β-oxidation and ROS generation. ROS induced increases in cytokine (TNFα and possibly other cytokines) expression and synthesis activates JNK which phosphorylates IRS-1 (insulin receptor substrate) at the serine[307] residue. This inhibitory phosphorylation of IRS-1 prevents its tyrosine phosphorylation by the insulin receptor and interferes with the normal insulin signalling cascade (Illustration modified from review by Rutledge and Adeli [22].

The experimental evidence implicating inflammation/pro-inflammatory cytokines and overactive renin-angiotensin systems (organ and systemic) in the aetiology of insulin resistance will be discussed later. We will first review the evidence for a role for elevated circulating free fatty acids, and tissue triglycerides and lipid intermediates accumulation in the aetiology of insulin resistance in skeletal and heart muscle.

4. The role of free fatty acids and intracellular lipid accumulation in insulin resistance

A prevalent metabolic change associated with obesity [44-49] and high fructose feeding [22-24] is the increase in the circulating free fatty acids and triglycerides. Under conditions of over-nutrition and dyslipidaemia, not all fatty acids entering the cell are utilized for oxidative purposes. Long chain fatty acyl-CoA accumulation provides substrates for non-oxidative processes such as triglyceride, diacylglycerol (DAG) and ceramide synthesis [50, 51]. In the myocardium lipid accumulation is a direct result of a mismatch between fatty acid uptake and oxidation by the cell [47, 52]. What is not clear is whether this accumulation is due to: 1) increased FFA uptake by the heart 2) compromised FFA oxidation, or, 3) a combination of the two.

There is a strong link between increased circulating free fatty acids, myocardial triglyceride accumulation and insulin resistance. Increased circulating free fatty acids increase the expression of sarcolemmal fatty acid transporters and increases fatty acid uptake into the myocyte. Obese Zucker rats [46, 48] and *db/db* mice [53] with insulin resistance have increased FAT/CD36 localised to the sarcolemma. The exact mechanism for the increased localisation of FAT/CD36 in the sarcolemma is not clear but may relate to the chronic hyperinsulinaemia associated with insulin resistance. It is well established that insulin stimulates FAT/CD36 translocation to the sarcolemma [54, 55]. This increased sarcolemmal FAT/CD36 content increases fatty acid uptake in cardiac myocytes and possibly leads to tissue fatty acyl-CoA accumulation if not metabolised through concomitant increased β-oxidation [56]. Besides its adverse effects on insulin signalling and glucose metabolism, excessive intramyocellular lipid accumulation may also have direct lipotoxic effects [50, 57]. Both altered substrate utilization and excess intramyocardial lipid accumulation which is characteristic of obesity, dyslipidaemia and insulin resistance may have serious cardiac consequences that ultimately lead to compromised cardiac metabolism, morphology and mechanical function.

Lipid intermediates may adversely influence insulin signalling and contribute to insulin resistance [5, 58, 59]. The accumulation of triglycerides, diacylglycerol (DAG) and ceramide is known to activate kinases that down-regulate insulin signalling [60-62]. These kinases include JNK, IKK and protein kinase C (PKC) that is known to inhibit insulin signalling via serine phosphorylation of IRS-1 [5, 63].

Ceramide accumulation occurs through *de novo* synthesis from saturated fatty acids [64] or hydrolysis of sphingomyelin [65]. It has been shown to cause insulin resistance by inhibiting Akt phosphorylation in skeletal muscle [66-68] and adipocytes [69] with the

pharmacological inhibition of ceramide synthesis being effective in preventing lipid induced insulin resistance in rats [67, 70].

Models of lipotoxicity have also demonstrated that elevated myocardial ceramide levels are associated with increases in indices of apoptosis [52, 71]. Rat neonatal cardiomyocytes incubated with physiological concentrations of palmitate have increased intracellular triglycerides, increased ceramide levels and increased indices of apoptosis [72]. The mechanism implicated in ceramide induced apoptosis may involve activation of NFκB which in turn up regulates inducible nitric oxide synthase (iNOS) expression [73]. The resulting increase in nitric oxide production [74] may cause a subsequent rise in the formation of peroxynitrite, which induces mitochondrial cytochrome C release [75] and subsequent apoptosis. In addition, ceramide has been shown to directly induce the generation of damaging reactive oxygen species in the mitochondria [76]. Obese insulin resistant (prediabetic) Zucker rats also have elevated intramyocardial triglycerides which are accompanied by increased myocardial ceramide levels and cardiomyocyte apoptosis. These cellular alterations are present before the onset of diabetes and cardiac dysfunction [71]. Reducing myocardial lipid levels by treating the rats with peroxisome proliferator-activated receptor gamma (PPARγ) agonists lead to reduced cardiac ceramide levels and apoptosis and prevented cardiac dysfunction [71]. In a similar study, mice over-expressing cardiac specific long chain acyl-CoA synthase display high intramyocardial triglycerides and ceramide levels. These changes were accompanied by increased DNA fragmentation and cytochrome C release with the mice developing cardiac hypertrophy and left-ventricular dysfunction [52].

Lipid infusion increases intracellular DAG and causes skeletal muscle insulin resistance in rodents [60]. This association between intracellular DAG levels and skeletal muscle insulin resistance has been confirmed in several rodent and human studies [77-79]. Increased muscle DAG is associated with increased activation of protein kinase C theta (PKC-θ) in obese and diabetic patients [80, 81]. Increased PKC-θ activation interferes with insulin signalling by increasing IRS-1 serine[307] phosphorylation (Figure 3)[60, 81]. Accelerating fatty acid oxidation rates potentially prevents fatty acid, acetyl-CoA and subsequent DAG accumulation and may improve insulin sensitivity. This proposal was recently supported by a study showing that carnitine palmitoyltransferase I (CPT-1) over-expression in L6E9 myotubes increases mitochondrial fatty acid uptake, decreased intracellular DAG concentrations and protects against elevated fatty acid induced insulin resistance [82].

4.1. Evidence for lipid accumulation in skeletal muscle insulin resistance

An inverse correlation exists between intramuscular lipid content and insulin sensitivity. Measurements of insulin sensitivity (120 min euglycaemic hyperinsulinaemic clamp) in skeletal muscle from healthy subjects demonstrated that high intramuscular lipid content was associated with lower whole body insulin stimulated glucose uptake. These subjects also exhibited elevated circulating free fatty acids, reduced tyrosine phosphorylation of the insulin receptor (IR) and lower (insulin receptor substrate) IRS-1 mediated PI3K activation during hyperinsulinaemia than subjects with low intramuscular lipids [83]. Studies

comparing lean and obese individuals have made similar observations linking intracellular lipid accumulation to skeletal muscle insulin resistance [84, 85]. Boden and colleagues [86] reported a strong association between serum free fatty acid levels, intramuscular lipid content and insulin resistance after lipid injection in healthy subjects. Elevated circulating free fatty acid levels, induced by lipid injection, was associated with a gradual increase in intramuscular lipid content and a 40% increase in insulin resistance. These observations also corroborated earlier studies demonstrating that elevated fatty acids reduced skeletal muscle glucose uptake in humans [87].
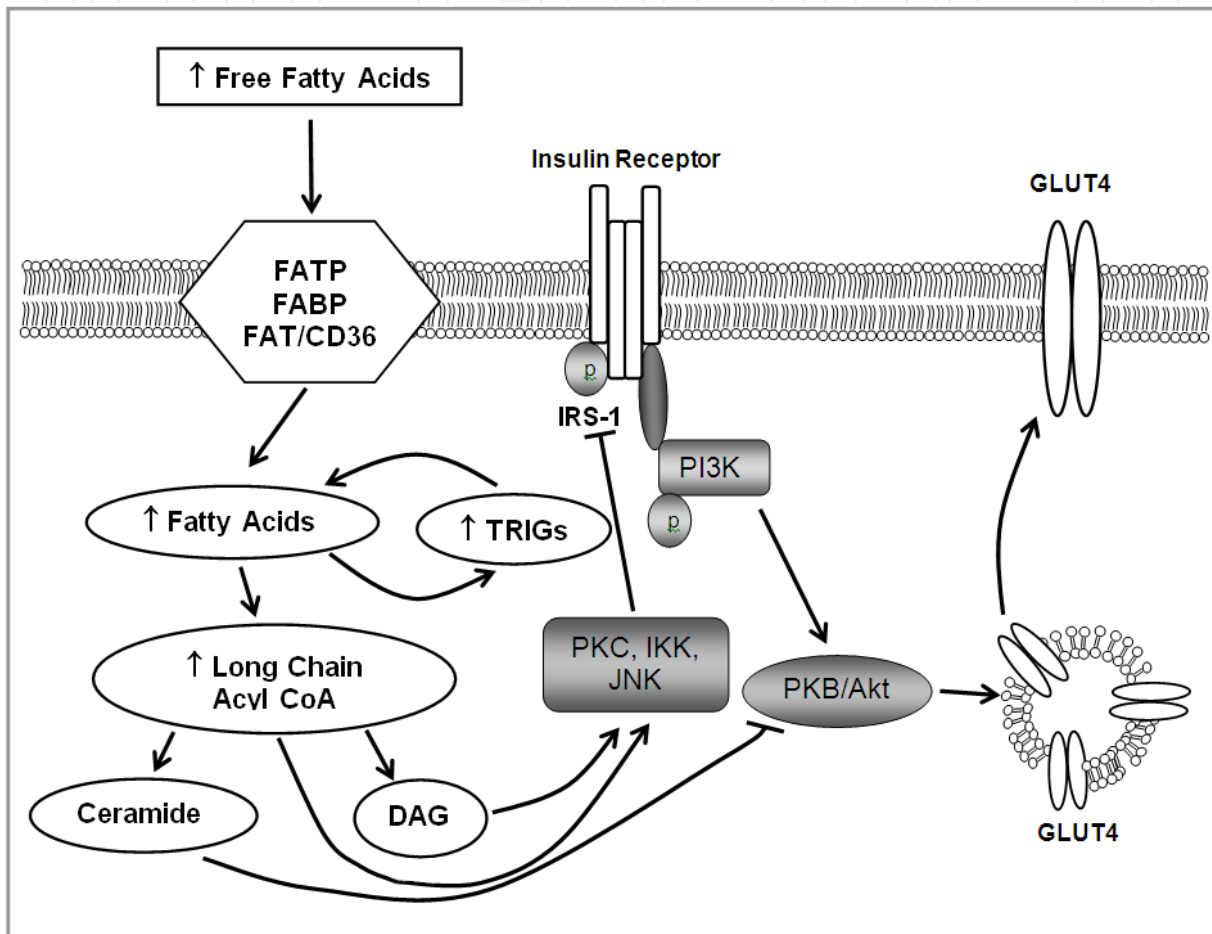
Figure 3. The proposed mechanism for dyslipidaemia induced insulin resistance. Increased circulating free fatty acids as occurs during overfeeding/obesity and/or high fructose diet feeding will increase fatty acid uptake. Long chain acetyl CoA not oxidised can be used in non-oxidative pathways with the generation of triglycerides, diacylglycerol (DAG) and ceramide. Both the latter lipid metabolites have been implicated in aetiology of insulin resistance through the activation of PKC, IKK and JNK.

In rodent skeletal muscle, experimentally elevated circulating free fatty acids increased intracellular acetyl-CoA and DAG levels which was coupled to increased active protein kinase C (PKC) theta. These changes were accompanied by increased IRS-1 serine phosphorylation, reduced IRS-1 tyrosine phosphorylation and reduced IRS-1 associated PI3K activity [60, 88]. Phosphorylation of IRS-1 at serine[307] evidently hinders IRS-1's interaction with PI3K and therefore interferes with normal insulin signalling.

4.2. Evidence for lipid accumulation in cardiac muscle insulin resistance

Similar associations between increased intracellular lipid accumulation and reduced insulin sensitivity have been observed in cardiac muscle from obese insulin resistant animals [47, 71, 89, 90]. In obese insulin resistant JCR:LA-cp rats, the increased supply of circulating free fatty acids was associated with a 50% increase in myocardial triglyceride content and a 50% reduction in myocardial glycolytic flux rates [89].

In humans, plasma free fatty acid levels correlate with intramyocardial triglyceride levels [91]. This association is also evident in obese [91, 92], obese glucose intolerant [93] and diabetic [93, 94] individuals. Excessive intramyocardial triglyceride accumulation precedes the development of type-2 diabetes and tends to increase linearly with the degree of systemic insulin resistance [93]. Obese insulin resistant humans do not always have elevated serum free fatty acid levels but do appear to maintain higher rates of free fatty acid uptake, utilization and subsequent oxidation than lean controls [95].

5. The role of cytokines and chronic inflammation in insulin resistance

Obesity and insulin resistance is associated with chronic systemic inflammation caused by activation of the intrinsic immune systems in organs and the macrophages that infiltrate them [96]. The most prominent pro-inflammatory mediators involved in this inflammation are TNFα and IL-6 that originate from: 1) macrophages in adipose tissue and the liver [97], 2) the adipocytes themselves [97], and, 3) several other cytokine synthesising tissues in the body [97-99].

Elevated free fatty acids may increase pro-inflammatory cytokine expression and synthesis since studies inducing acute increases in plasma free fatty acids have observed activation of NFκB in skeletal muscle in humans [79] and increases hepatic TNFα, IL-1β and IL-6 and circulating monocyte chemotactic protein-1 (MCP-1) in rats [100, 101]. How elevated fatty acid cause NFκB activation is unknown but may involve DAG and PKC [102] or the Toll-like receptor 4 (TLR-4) [103]. MCP-1 is also known to regulate recruitment of macrophages to sites of inflammation and may be involved in the recruitment and differentiation of monocytes to macrophages that produce pro-inflammatory cytokines in conditions such as obesity and dyslipidaemia [97, 104].

TNFα causes insulin resistance by suppressing IRS-1 associated insulin signalling and glucose transport in skeletal muscle while IL-6 activates the phosphatase SHP-2 and Signal transducer and activator of transcription 3 (STAT3) causing increased expression of suppressor of cytokine signalling 3 (SOCS3) [105, 106]. IL-6 also activates several serine/threonine kinases such as JNK, p38 mitogen activated protein kinases and PKC-δ that contribute to reduced insulin sensitivity and glucose metabolism (Figure 4) [107, 108].

Information relating to the possible role of inflammation in the aetiology of myocardial insulin resistance is limited. A recent study however reported that high fat feeding caused increased myocardial macrophage infiltration and increased cytokine and SOCS levels in cardiomyocytes from these animals [109]. These changes were associated with reduced myocardial insulin sensitivity and glucose metabolism.
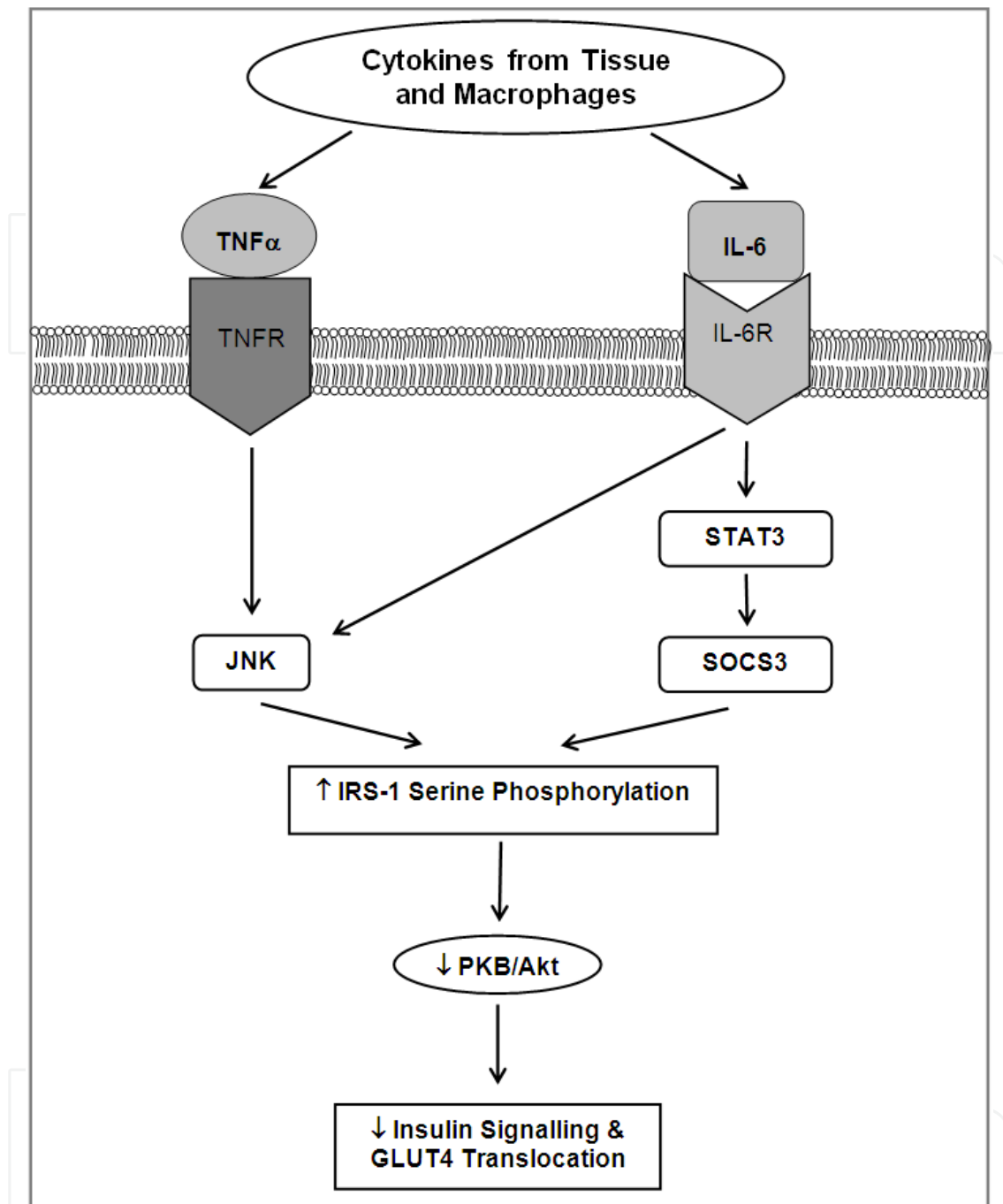
Figure 4. Proposed mechanism for inflammation induced insulin resistance in muscle. Cytokines from macrophages and myocytes activate their receptors and associated signalling pathways to increase serine (inhibitory) phosphorylation of IRS-1. IL-6 is known to activate the STAT3-SOCS3 pathways while TNFα activates JNK to phosphorylate IRS-1.

6. The role of the Renin-Angiotensin System (RAS) in insulin resistance

The authors [110] and others [111-115] have shown that the systemic and tissue renin-angiotensin systems (RAS) activity is increased in obesity. The role of increased RAS activity in metabolic and cardiovascular disease has been reviewed in detail [29, 116-118]. A key

observation linking the RAS system to insulin resistance was made when it became apparent that hypertensive patients treated with angiotensin converting enzyme (ACE) inhibitors or angiotensin (AT) receptor blockers have a reduced risk of developing insulin resistance and type-2 diabetes when compared to patients on other conventional anti-hypertensive therapy [119, 120]. Subsequent studies have corroborated these observations with RAS inhibition improving blood glucose management [121] and lowering risk of type-2 diabetes [122]. These data provided indirect evidence to suggest that the RAS (and particularly over-activation) contributes to insulin resistance and type-2 diabetes.

Several human and animal studies support a role for RAS over-activity in insulin resistance. Genetic abnormalities leading to over-activation of the RAS provides strong evidence for the involvement of the RAS in insulin resistance. In infants [123] and adults [124, 125] the DD genotype of the ACE I/D polymorphism is associated with glucose intolerance and insulin insensitivity. Similarly, AGTT174M polymorphisms are associated with metabolic syndrome in aboriginal Canadians [126].

As mentioned previously, pharmacological blockade of the RAS in clinical trials has provided the most compelling evidence for a role for RAS over-activity in metabolic abnormalities such as insulin resistance. The use of ACE inhibitors for antihypertensive therapy reduces the risk of developing type-2 diabetes by 14% [119]. Studies on animals support these observations with RAS inhibition improving insulin sensitivity in rat [127] and mice [128]. Genetic deletion of renin [129] or ACE [130] or one of the two AT receptors also appears to be effective in preventing or reducing insulin resistance in mice [131, 132].

Besides the evidence showing that inhibition of RAS activity may improve insulin sensitivity, several studies also provide direct evidence implicating over-activation of the RAS in the aetiology of insulin resistance. Chronic angiotensin II infusion causes insulin resistance in rats [133, 134] while the TG(mREN2)27 rat which suffers from chronic systemic RAS over-activation develops muscle and systemic insulin resistance [135]. The RAS induced insulin resistance in these animals is improved by renin inhibition or angiotensin receptor blockade [135, 136].

The mechanism for angiotensin II (Ang II) induced insulin resistance has received significant attention. Ang II adversely affects glucose metabolism and decreases its uptake and utilisation by interfering with insulin signalling [137]. In L6 myocytes Ang II suppresses insulin induced phosphorylation of the tyrosine residue on IRS-1. This was associated with decreased activation of PKB/Akt and GLUT4 translocation to the sarcolemma. These changes were all AT_1 receptor, NADPH oxidase and NFκB dependent [138, 139]. Based on these observations it seems likely that Ang II activates NADPH oxidase and increases reactive oxygen species (ROS) generation through the angiotensin type 1 (AT_1) receptor. ROS activate the NFκB to increase transcription of cytokines that include TNFα and IL-6. These cytokines increase SOCS3 expression which inhibits insulin signalling (Figure 5) [140]. In rats Ang II also reduces skeletal muscle mitochondrial content (possibly through increased ROS generation) which would be expected to reduce muscle glucose utilisation [141].
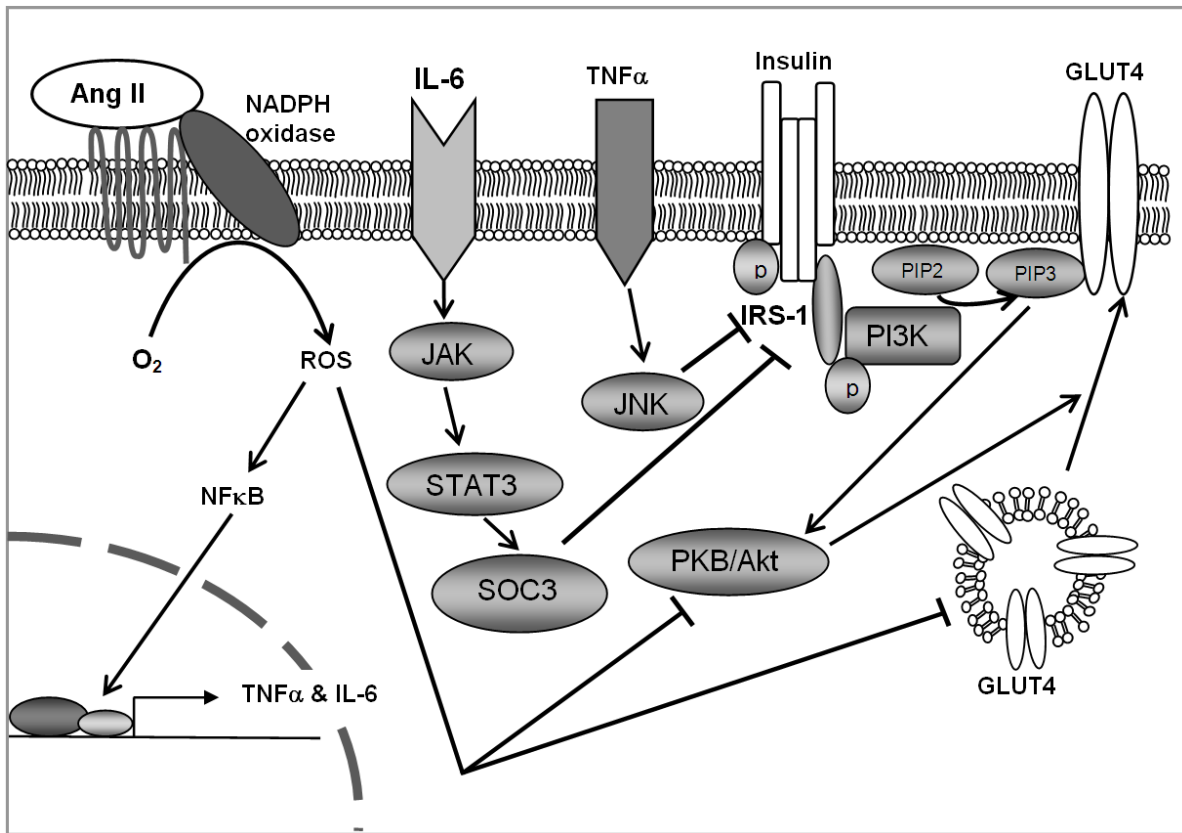
Figure 5. Proposed mechanism for renin-angiotensin system over-activation induced insulin resistance. Angiotensin II activates NADPH oxidase to generate reactive oxygen species (ROS) which activate the translocation of NFκB to the nucleus. Here it causes the transcription, synthesis and release of cytokines (TNFα and IL-6). The binding of these cytokines to their sarcolemmal receptors induce serine kinases and SOC3 which inhibits IRS-1 tyrosine phosphorylation, insulin signalling and GLUT4 translocation.

Adipose tissue RAS over-activity may also contribute to systemic insulin resistance since Ang II from adipose tissue contributes to circulating Ang II levels. This was well demonstrated by a study investigating the effect of adipose tissue angiotensinogen (Agt) over-expression on systemic glucose tolerance and insulin resistance [142]. The over-expression of Agt in adipose tissue caused cardiac and skeletal insulin resistance and reduced muscle glucose uptake.

7. The role of adipocytokines in the aetiology of insulin resistance

Adipocytokines released from adipose tissue perform regulatory functions in energy and fluid balance and satiety and have been implicated in conditions such as obesity, dyslipidaemia, insulin resistance/diabetes and cardiovascular disease. Besides the two pro-inflammatory cytokines discussed previously (TNFα and IL-6) adipocytes secrete several well characterised adipocytokines that include: leptin, adiponectin, and resistin. Dysregulation of the synthesis and secretion of these peptides has been associated with, and implicated in, the aetiology of metabolic diseases such as insulin resistance and type-2 diabetes. A possible role for adipokines in the regulation of myocardial metabolism only emerged recently [143-145].

Leptin is synthesised by white adipose tissue and is involved in appetite control and energy expenditure. Although the absence of leptin leads to obesity and insulin resistance, most obese patients have elevated leptin levels but do not respond to the appetite suppressing and other effects of the peptide [146, 147]. Mutations of the leptin receptor (Ob-R) are associated with obesity in the *db/db* mouse [148] and the Zucker (*fa/fa*) rat [149] and leptin deficiency occurs in obese (*ob/ob*) mice [150] while the treatment of patients [151, 152] and animals [150] with recombinant leptin reduces body weight and improves serum lipid levels.

Serum triglyceride levels and blood glucose handling also improved in women with lipodystrophy and leptin deficiency indicating that leptin may alter lipid metabolism and prevent lipotoxicity [153]. Animal studies demonstrate that leptin promotes lipid oxidation. In rat adipocytes leptin reduces insulin's' lipogenic effect by: 1) inhibiting insulin binding to its receptor [154], 2) increasing adipose and non-adipose tissue β-oxidation, and, 3) decreasing adipose tissue triglyceride content without elevating circulating free fatty acids (Figure 6) [74]. This reduction in serum fatty acid levels will also counter the effect of insulin on lipogenesis [74, 154].
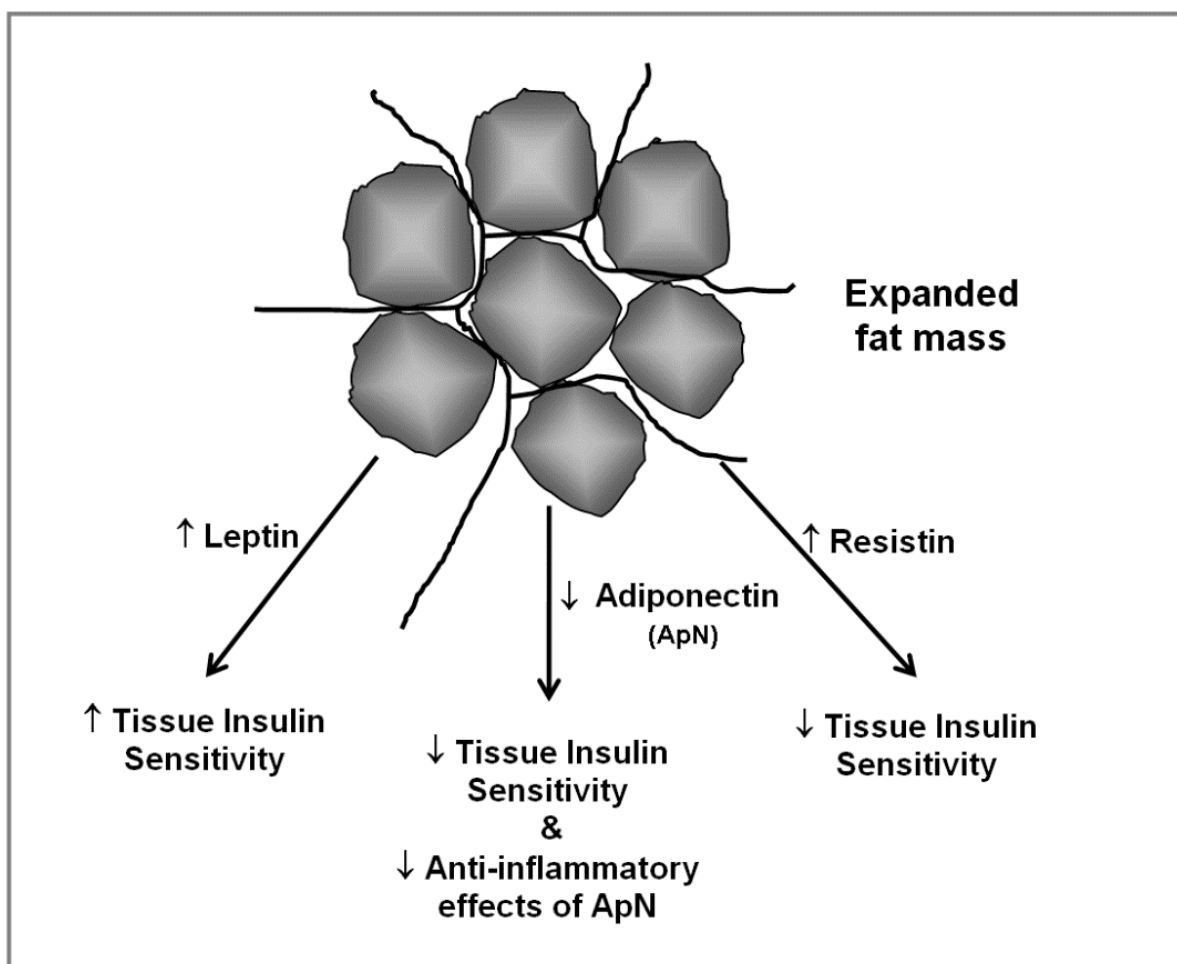
Figure 6. A simplified illustration to demonstrate the effects of adipocytokines on tissue insulin sensitivity and inflammation.

There is a strong association between leptin deficiency/resistance and lipotoxicity [155]. The lipid lowering effects of leptin in heart muscle was demonstrated in a study where 24 hour high fat feeding of mice was associated with cardiac lipid accumulation in animals with low leptin levels but not those with high plasma leptin levels [156]. Leptin administration decreases cardiac muscle lipotoxicity in a subsequent study by this group [157].

Leptin administration to the perfusate of isolated rat hearts perfused with palmitate and glucose significantly increased fatty acid oxidation and reduced intramyocardial triglyceride content without increasing cardiac work. This was accompanied by increased myocardial oxygen consumption and reduced cardiac efficiency [143]. The significance of leptin in metabolism is further highlighted in genetic models such as the leptin deficient *ob/ob* mouse and the leptin resistant *db/db* mouse that has a loss-of-function mutation on the leptin receptor. These animals are obese, insulin resistant and display excess intramyocardial lipid accumulation. They are also more prone to increased cardiomyocyte apoptosis and cardiac dysfunction than their control littermates [158-162].

Circulating adiponectin levels are reduced in obesity, insulin resistance and diabetes and correlate with the extent of insulin resistance and hyperinsulinaemia [163-165]. It is synthesised by adipocytes, skeletal muscle, heart muscle and endothelial cells [166] and is a key adipocytokine in the regulation of metabolism. It is considered to be an anti-diabetic, anti-inflammatory and anti-atherogenic agent with adiponectin deficient animals becoming glucose intolerant, insulin resistance and hyperleptinaemic [167, 168]. Studies utilising adiponectin replacement therapy have demonstrated its ability to decrease dyslipidaemia [169] and improve insulin sensitivity (Figure 6) [170-172].

Adiponectin acts via phosphorylation of 5'adenosine monophosphate-activated protein kinase (AMPK) to influence insulin sensitivity and fatty acid and glucose utilisation [172, 173]. Its action is mediated through the AdipoR1 and AdipoR2 receptors [170] that are both expressed in cardiac tissue [174]. Receptor activation is associated with modulation of AMPK, PI3K, p38 MAP kinase and extracellular signal-regulated kinase (Erk) 1/2 MAP kinase [175-177].

Resistin is secreted from white adipose tissue but is also expressed in other tissues [178]. It was given its name because it was originally shown to counter the effects of insulin by suppressing insulin signalling [179]. Over-expression of resistin is associated with dyslipidaemia and insulin resistance [180, 181] and inhibition of glucose uptake in cardiomyocytes [182]. In humans plasma resistin levels are closely correlated to insulin resistance irrespective of body weight [183]. However, these observations are not supported by two animal studies that found that resistin levels were not a good predictor of insulin resistance when corrected for body mass index (BMI) [184, 185]. In both high fat diet and genetic mutation induced obesity, resistin levels were closely associated with body weight with obese animals having significantly elevated resistin levels [179]. The exact role of resistin in insulin resistance is however poorly understood and unresolved.

8. Effects of myocardial insulin resistance on myocardial metabolism, mechanical function and tolerance to ischaemia and reperfusion

The heart utilises glucose, fatty acids and lactate as fuels for the production of ATP. Cardiac metabolism is under the control of several hormones with insulin being a key regulator of glucose, fatty acid and lactate metabolism. Changes in myocardial insulin sensitivity disrupt the hearts' normal substrate metabolism and potentially decrease mechanical function and myocardial tolerance to ischaemia/reperfusion.

8.1. Myocardial metabolism

The heart is a dynamic organ, constantly requiring energy in the form of ATP in order to meet its homeostatic and contractile demands. This is achieved through a constant supply of oxidizable substrates from the circulation. The most important substrates utilized by the heart are: fatty acids, glucose and lactate. Although the adult heart is capable of oxidizing a variety of substrates, the majority of ATP (60-70%) generated by the heart originates from the oxidation of fatty acids [186, 187]. However, in the presence of elevated glucose and insulin levels as occurs immediately following a meal, 60-70% of ATP may be derived from glucose metabolism [188].

Circulating fatty acids are taken up by the heart either in their free form (as free fatty acids (FFAs)) bound to albumin, or they can be released from the triglyceride component of chylomicrons or very-low-density-lipoproteins (VLDL) [189]. The concentration of fatty acids present in blood greatly dictates their uptake and metabolism by the heart [190]. Under normal physiological conditions, long chain fatty acids (LCFAs) are the principal fatty acids oxidized by the heart [191]. The entry of LCFAs across the sarcolemma into the cytoplasm of the cardiomyocyte occurs though passive diffusion or membrane protein mediated transport, the latter accounting for the majority of fatty acid translocation to the cytosol [192]. This membrane protein mediated transport is facilitated by fatty acid translocase (FAT)/CD36, plasma membrane fatty acid binding protein (FABPpm) and fatty acid transport protein (FATP) [192]. Once inside the cell, non-esterified LCFAs are transported via cytoplasmic heart-type FABPs through the cytoplasm to the location where they will be utilized [193-195]. LCFAs are then esterified by acyl-CoA synthetase to form long chain fatty acyl-CoA's (LCFA-CoA) [55]. LCFA-CoAs can be stored in intracellular lipid pools where they can be converted to additional lipid intermediates (triglycerides, diacylglycerol (DAG) or ceramide), or are transported to the mitochondria where they undergo β-oxidation.

Glucose enters the cardiomyocyte through either the basal uptake glucose transporter, GLUT1, or via the insulin dependent glucose transporter, GLUT4 [196]. GLUT4 is stored in cytoplasmic vesicles which are recruited to the sarcolemma in response to insulin stimulation or cardiac contraction. Glucose itself can also induce GLUT4 translocation with this and insulin stimulated translocation determining the glucose flux rate into the cardiomyocyte [197]. Inside the cell hexokinase converts glucose to glucose-6-phosphate which can be stored as glycogen (after conversion by glycogen synthase) or it can undergo

glycolysis to yield pyruvate and ATP. During adequate myocardial oxygen availability pyruvate is transported into the mitochondria via a mitochondrial monocarboxylate transporter [198] and subsequently oxidized by pyruvate dehydrogenase (PDH) to produce acetyl-CoA (reviewed by Stanley *et al*. [199]). During anaerobic conditions as occurs during myocardial ischaemia, pyruvate may be converted to lactate.

The rate of glucose oxidation is also influenced by fatty acid β-oxidation rates since hexokinase, PFK and PDH activity are all inhibited by various products of fatty acid metabolism (for a review see Hue and Taegtmeyer [200]). There is a delicate interplay in the utilisation of these two myocardial substrates which is intricately related to their circulating levels. The common endpoint where glucose and fatty acid metabolism converge is the production of acetyl-CoA which enters the tricarboxylic acid/Krebs cycle where it is used to generate ATP during oxidative phosphorylation [187, 201]. Alternatively the acetyl-CoA can be utilised in non-oxidative pathways for the production of triglycerides, DAG and ceramide.

8.2. Impact of myocardial insulin resistance on myocardial metabolism

The early onset of insulin resistance in obesity may be a physiological response to increased lipid availability leading to increased lipid utilisation and a reciprocal reduction in glucose metabolism. Chronic dysregulation of glucose uptake and metabolism by dyslipidaemia and inflammation may however induce pathological changes in cardiac metabolism that compromise cardiac morphology and mechanical function.

High fat feeding of C57BL/6 mice induces myocardial insulin resistance within 10 days. This insulin resistance was associated with reduced myocardial glucose uptake, PKB/Akt activity and GLUT4 protein levels and preceded and occurred independently of systemic insulin resistance [202]. With myocardial insulin resistance, fatty acid oxidation rates are normal or elevated, while glucose oxidation rates are normally reduced both in the presence or absence of insulin stimulation [5, 44, 45, 203-205]. Although a limited number of studies have reported similar myocardial fatty acid and glucose oxidation rates in obese, insulin resistant animals when compared to lean controls, they have all found that insulin stimulated myocardial glycolytic flux rates remain suppressed with insulin resistance [89, 206]. In humans similar increases in myocardial fatty acid metabolism were reported in obese men and women. Gender however also played and important role in determining the impact of obesity of glucose and fatty acid uptake and utilization [207]. Women were less prone to obesity induced dysregulation of myocardial metabolism than their obese male counterparts. These gender based differences in myocardial metabolism in response to obesity may translate to differences in the development of obesity-related cardiovascular diseases.

8.3. Effect of insulin resistance on cardiac mechanical function

Increased lipid uptake and oxidation as seen with insulin resistance potentially leads to cellular lipid intermediate accumulation, excessive mitochondrial or peroxisomal ROS generation and functional derangement in the heart [71]. This is well demonstrated by a

study showing that cardiac specific PPARα over-expression which increases cardiac lipid oxidation causes metabolic derangements and leads to adverse structural and function changes in the heart [208]

Pre-diabetic (insulin resistant) obese Zucker rats display cardiac dysfunction [47]. These observations were corroborated in obese insulin resistant mice (ob/ob and db/db) that had increased myocardial lipid oxidation rates, decreased glucose oxidation rates and decreased cardiac efficiency. These changes were also associated with systolic dysfunction when compared to lean insulin sensitive littermates [45].

Although genetic models of obesity do not accurately resemble the phenotype of human obesity, the recent development of a number of models of diet-induced obesity have contributed to a better understanding of the impact of obesity and insulin resistance on myocardial function. High fat feeding induced insulin resistance in C57BL/6 mice also causes cardiac remodelling and systolic dysfunction [202]. The authors and other research groups have however also shown that rodent models of diet-induced obesity with insulin resistance have either normal [90, 203, 205, 209, 210] or compromised [110, 203, 204, 211, 212] cardiac mechanical function. It is currently not possible to conclusively attribute the cardiac dysfunction reported in these studies to myocardial insulin resistance since there are several studies that have reported normal cardiac function in animal models with insulin resistance [90, 203, 205, 209, 210].

Reduced cardiac efficiency possibly contributes to cardiac dysfunction in obesity, insulin resistance and diabetes [44, 45, 213]. Animals [44, 45, 162, 213] and humans [95] that are obese and insulin resistant or diabetic have increased myocardial oxygen consumption which reflects a decreased cardiac efficiency as determined by the myocardial work to myocardial oxygen consumption ratio [214]. Mitochondria isolated from obese insulin resistant mice have reduced oxidative capacity, and display fatty acid induced uncoupling of mitochondrial oxygen consumption and ATP production which is evident from the reduced ATP-to-O ratios [162, 213]. This data from human and rodent studies also implicate impaired mitochondrial energetics in the cardiac dysfunction associated with obesity and insulin resistance. Recent epidemiological evidence points to an important mediatory role for insulin resistance in the development of obesity related congestive heart failure [215].

8.4. Effect of dyslipidaemia and insulin resistance on myocardial tolerance to ischaemia/reperfusion

A key feature of myocardial ischaemia is the reduced oxygen and substrate availability that results in lower mitochondrial oxidative phosphorylation rates. Ischaemia essentially disrupts the tightly coupled ATP breakdown and re-synthesis equilibrium that exists during normoxia and leads to an ATP deficit. Cellular ATP becomes depleted with the extent of this depletion being dependent on the duration and severity of ischaemia [216].

Although oxidative metabolism is reduced during ischaemia, reperfusion after ischaemia is associated with an initial increase in glycolytic flux rate which quickly declines to normal levels [217]. Despite glycolysis only accountings for a small amount of the total ATP

production under aerobic conditions, glycolytically generated ATP becomes invaluable in the maintenance of cellular ion pump function and ion homeostasis and the reduction of myocardial damage during mild ischaemia [218]. While glycolytically produced ATP may aid in maintaining ion homeostasis during ischaemia, it is insufficient for the maintenance of myocardial contractile function [218]. Under conditions of severe ischaemia in the absence of a glucose and oxygen, myocardial glycogen stores undergoing glycolysis do not only contribute to the ATP synthesised, but greatly increase cytosolic proton accumulation and a decline in intracellular pH [219]. Despite its potential adverse effect on pH, elevated glycogen levels at the onset of myocardial ischaemia may be important in maintaining tissue ATP levels since it has been associated with improved functional recovery after ischaemia [220].

Despite myocardial ischaemia decreasing mitochondrial substrate oxidation, fatty acid oxidation predominates during ischaemia and subsequent early reperfusion [221]. During early ischaemia there is a transient increase in anaerobic glycolysis while glucose oxidation decreases [199, 221-224]. Under these conditions normal or increased glucose uptake (under the influence of insulin) may be important for the delivery of glycolytic ATP to maintain ion homeostasis. Hearts from animal models of obesity and insulin resistance [211], isolated insulin resistance [225] and diabetes [226] have a reduced tolerance to ischaemia and reperfusion and suffer more severe ischaemia/reperfusion injury. Myocardial insulin resistance potentially decreases myocardial tolerance to ischaemia by decreasing glucose uptake, glycogen synthesis and glycolysis which all play a critical role in the delivery of ATP for cellular homeostasis in the ischaemic/reperfused heart.

Although fatty acids are predominantly oxidized by the ischaemic heart, the preference for fatty acid oxidation as occurs under dyslipidaemic conditions also has adverse effects on the ischaemic and reperfused heart. The mitochondrion generates 12% less ATP per oxygen molecule through the oxidation of fatty acids compared to glucose oxidation during normoxia [187]. Increased fatty acid oxidation consequently reduces cardiac efficiency during ischaemia and subsequent reperfusion. During reperfusion the glycolytic flux rate exceeds glucose oxidation rates which remains suppressed due to increased fatty acid oxidation during reperfusion [224, 227]. This fatty acid induced uncoupling of glucose oxidation from glycolysis results in an accumulation of hydrogen ions which can damage the heart and affect post ischaemic function [199, 228-230]. These detrimental effects of increased fatty acid β-oxidation during both ischaemia and reperfusion would be expected to be pronounced in dyslipidaemia (as occurs in obesity and high fructose feeding) and insulin resistance and exacerbate ischaemic injury.

Pharmacological inhibition of myocardial fatty acid oxidation prior to the onset of, or during reperfusion results in increased glucose oxidation and improved cardiac functional recovery following the ischaemic episode [224, 227]. Hearts from prediabetic obese Zucker rats have reduced GLUT4 expression, reduced glucose uptake and larger reductions in tissue ATP levels during low-flow ischaemia. These changes are associated with poorer post-ischaemic functional recoveries when compared to their lean control littermates [231]. Treating these rats with rosiglitazone (the insulin sensitizer) normalized myocardial total GLUT4 protein expression, myocardial ischaemic substrate metabolism and improved reperfusion functional recovery.

8.5. The effect of insulin resistance on myocardial pro-survival signalling and ischaemic tolerance

The ability of the heart to withstand injury during ischaemia and reperfusion is not only dependent on myocardial metabolism but also upon the expression and functionality of its intrinsic pro-survival signalling pathways. Investigations into cardioprotection with preconditioning and postconditioning has revealed common signalling elements that transduce protective stimuli and converge on mitochondrial targets [232-234]. These stimuli recruit paths comprising cell surface G-protein coupled receptors (GPCRs), signalling kinase networks (*e.g.* PI3K-Akt-eNOS, Erk1/2, PKC, p38-MAPK, Glycogen synthase kinase 3 beta (GSK3β)) that have been dubbed the Reperfusion Injury Salvage Kinases (RISKs), and mitochondrial components that may represent end-effectors. These end-effectors include K_{ATP} channels and the mitochondrial permeability transition pore - mPTP (Figure. 7). Central to the RISK pathways is protein kinase B (PKB)/Akt which is not only key to myocardial insulin signalling [188] and physiological hypertrophy/remodelling [235] but is also considered a pro-survival/anti-apoptotic kinase in the context of myocardial ischaemia/reperfusion.
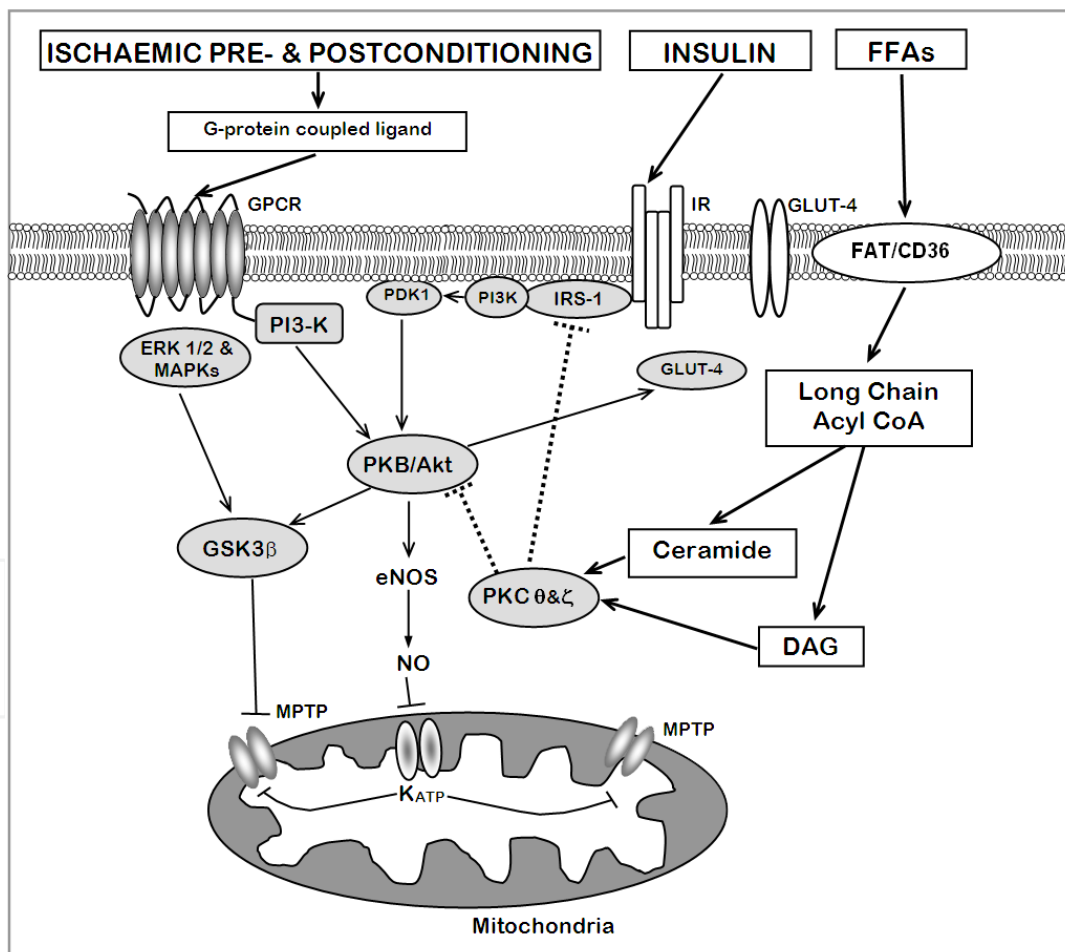
Figure 7. An illustration demonstrating the pivotal role of PKB/Akt in the RISK and insulin signalling pathways and the possible impact of dyslipidaemia and insulin resistance on these signalling pathways. Broken line represents the proposed mechanism linking insulin resistance with PKB/Akt inhibition/inactivation and Reperfusion Injury Salvage Kinase (RISK) pathway dysfunction.

Insulin regulates cardiac metabolism, growth and mitogen-activated protein kinase (MAPK) pathways through pivotal PKB/Akt. Dyslipidaemia induced insulin resistance which is characterized by PI3K/Akt dysregulation possibly also negatively influences the functionality of the RISK pathway in the heart during ischaemia/reperfusion.

Early experimental evidence has emerged to support a role for obesity with insulin resistance in RISK pathway dysfunction. Wagner and co-workers [236] have shown loss of preconditioning in a rat model of established metabolic syndrome. In the leptin-deficient (*ob/ob*) mouse cardiac benefit from postconditioning is impaired [237], while there is also evidence of failed preconditioning in obese insulin-resistant rats [238]. Failure of a variety of cardioprotective interventions involving multiple and varied triggers, implicates dysfunction of the signalling paths of the RISK pathway that are common to these interventions. This is also supported by the recent findings of Bouhidel and co-workers [237] who reported impaired phosphorylation of Akt, Erk1/2 and p70S6K1 in *ob/ob* mice while others [236] presented evidence of impaired Erk1/2 activation and failure to phosphorylate and inactivate GSK3β. Ineffective protection in obese insulin resistance rats is also associated with impaired activation of the mitochondrial K$_{ATP}$ channel [238]. All early indications suggest that distinct changes in intrinsic cardioprotective signalling occur in myocardial insulin resistance.

9. Interventions and therapy for the treatment of insulin resistance

Compelling scientific evidence indicates that obesity and/or lipogenic diets that lead to dyslipidaemia promote insulin resistance. Besides the dyslipidaemia, abnormal RAS activity and perturbations in adipocytokine levels also contribute to tissue insulin insensitivity. The primary goal of therapy for the treatment of insulin resistance should therefore be to prevent or reduce obesity (adipose tissue expansion) and dyslipidaemia. In addition to normalising circulating lipid levels, weight loss would normalise adipose tissue content and its associated pro-inflammatory cytokine and adipocytokine levels and ultimately improve insulin resistance. Since there is a direct correlation between obesity and RAS over-activation, weight loss and/or RAS inhibition has the potential to attenuate the adverse effects of abnormal RAS activity on tissue insulin signalling.

9.1. Lifestyle changes: Physical activity and diet

Maintaining normal body weight or reducing body weight in overweight patients is the preferred approach for the prevention or treatment of the underlying causes of insulin resistance. Regular physical activity aimed at balancing caloric intake with caloric expenditure is recommended to maintain body weight. To reduce body weight caloric intake should be reduced and caloric expenditure increased until the desired body weight has been achieved. Current recommendations are to do 30 minutes moderate intensity exercise daily in order to maintain normal body weight and reduce the risk of developing medical conditions such as cancer, insulin resistance, diabetes and cardiovascular disease [239].

In addition to regular exercise to maintain normal body weight or promote weight loss, individuals with a genetic predisposition to obesity, insulin resistance and diabetes should

carefully manage their diet and reduce their intake of refined sugars, trans- and saturated fats and cholesterol and increase their consumption of grains, and fruit and vegetables [240]. Based on recent evidence provided by studies investigating the potential role of fructose in dyslipidaemia and metabolic diseases [24, 27, 41], it would also be prudent to avoid the overconsumption of fructose rich foods and beverages.

The larger the BMI loss achieved through exercise and/or dietary restriction, the larger the metabolic improvements that are achieved. Weight loss improves lipid profiles and blood glucose levels in metabolic syndrome patients [241] with a weight loss of more than 10% reversing metabolic disorders in two-thirds of metabolic syndrome patients studied [242]. These patients no longer met the criteria for metabolic syndrome. Lifestyle interventions also decreases the progression from insulin resistance to type-2 diabetes. In the US Diabetes Prevention Program, interventions aimed at reducing body weight by 7% succeeded in preventing progression from insulin resistance to type- 2 diabetes by 58% [243]. In this study 38% of the patients with metabolic syndrome at entry into the study had a reversal of metabolic syndrome with body weight loss.

9.2. Drug therapy that improves insulin sensitivity

Although lifestyle changes should remain the therapy of choice for the reduction of body weight and normalisation of metabolic disorders, not all patients respond to lifestyle changes to the same extent. In many cases lifestyle changes fail to achieve the intended objective of adequate weight loss. Under these circumstances pharmacological interventions have to be considered. Several drugs have been developed to improve lipid profiles and insulin sensitivity/action but have been disappointing and have in some cases had adverse side effects.

9.2.1. Lipid lowering drugs

Dyslipidaemia which presents as elevated circulating triglycerides and LDL-cholesterol and low HDL-cholesterol can be treated with statins (3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors) that reduce levels of all forms of Apo B containing lipoproteins [244-247]. These drugs reduce the conversion of acetyl-CoA to mevalonate and the eventual synthesis of cholesterol in the liver by blocking HMG-CoA reductase. There are several studies that have demonstrated that statins (simvastatin and atorvastatin) improve plasma triglyceride and glycosylated haemoglobin in non insulin dependent diabetics [246]. Fluvastatin also improved lipid profiles and insulin resistance in nondiabetic dyslipidaemic patients. These researchers however concluded that the insulin sensitising effects of fluvastatin were not related to its triglyceride lowering effects [247].

Another class of lipid lowering drug that has achieved satisfactory results is the fibrates that activate peroxisome proliferator-activated receptor (PPARs) and facilitate lipid metabolism. In humans, fibrates lower circulating triglyceride and LDL-C levels [248, 249] and elevate HDL-C levels [249]. PPARα agonists possibly improve lipid profiles by increasing the synthesis of both apolipoprotein A-I [248] and A-II [250] which would assist in increasing HDL-cholesterol

while reducing apolipoprotein B which is a major lipoprotein constituent of LDL-cholesterol. PPARα agonists also increase hepatic mitochondrial β-oxidation which reduces hepatic free fatty acids that are an essential component of VLDL and LDL-cholesterol.

Since PPARα agonists have repeatedly been demonstrated to have both systemic and tissue specific insulin sensitizing effects [251-254] their potential for the treatment of insulin resistance and diabetes is encouraging. The insulin sensitising effects of the fibrates probably relate to their lipid lowering effects since a PPARα agonist significantly increases hepatic and skeletal muscle insulin receptor and IRS-1 tyrosine phosphorylation, while increasing IRS-associated PI3K activity in obese (*ob/ob*) mice [252]. These insulin sensitising effects were accompanied by reduced hepatic, skeletal muscle [252] and heart muscle [255] lipid accumulation.

Combination therapy using statins and fibrates has been an attractive possibility but the results have been disappointing. The fibrate gemfibrozil in combination with statins has been associated with increased risk of myopathy [256]. It has however been proposed that the adverse effects of gemfibrozil and statin combination therapy may be due to a pharmacological interaction between these two drugs and that other fenofibrates may be more suitable for combination therapy with statins [257].

9.2.2. Insulin sensitizers

The two most promising insulin sensitizers are metformin and the glitazones. Metformin decreases hepatic gluconeogenesis and triglyceride production which in turn enhances insulin sensitivity [258]. Metformin reduced the progression of insulin resistance (pre-diabetic) to type-2 diabetes in the Diabetes Prevention Program [243].

Thiazolidinediones (TZDs) are PPARγ agonists that regulate insulin sensitivity in the liver, muscle and adipose tissue by increasing fatty acid oxidation and decreasing fatty acid synthesis [258]. TZDs are also believed to have anti-inflammatory effects. Pioglitazone was used in the ACT-NOW study in which it improved HDL-cholesterol and triglyceride levels and reduced the incidence of type-2 diabetes by 78% in prediabetic patients followed up over 2 years [259]. The Pioglitazone In Prevention Of Diabetes (PIPOD) study demonstrated that pioglitazone reduced the incidence of diabetes in premenopausal women [260]. It similarly improves insulin sensitivity and reduces both blood FFA and triglycerides levels in obese non-diabetic patients [261]. The usefulness of pioglitazone for the management of insulin sensitivity is however limited since it promotes fluid retention which increases risk of heart failure in certain patient populations with cardiovascular disease. In the diabetes reduction assessment with ramipril and rosiglitazone medication (DREAM) trial, rosiglitazone showed potential in preventing diabetes but appeared to increase the risk of heart failure [262].

9.2.3. RAS inhibitors or AT receptor blockers

Obesity and high fat feeding increases both systemic and adipose tissue RAS activity [110, 112-115]. As discussed previously in this chapter, the most compelling evidence for a role

for the RAS in the aetiology of insulin resistance comes from studies using ACE inhibitors and AT receptor antagonists to control blood pressure. Both these therapies are associated with reduced risk of developing insulin resistance and type-2 diabetes in patients [119, 122, 263-266] and in rodent models of obesity and insulin resistance [127, 128]. Although these antihypertensives are not prescribed for the treatment of abnormal RAS activity, they potentially improve insulin sensitivity in a patient population that is at high risk of cardiovascular disease due to their hypertension.

9.2.4. Anti-inflammatory therapy

Several lines of evidence implicate chronic inflammation in the aetiology of insulin resistance. Obesity is associated with elevated circulating cytokines and C-reactive protein which can be normalised by weight loss [267]. Although no drugs are currently available to treat chronic systemic inflammation, the use of lipid lowering drugs have been associated with reduced C-reactive protein levels in patients [267-269]. These drugs are not prescribed to specifically reduce inflammation but may contribute to improved insulin sensitivity by improving dyslipidaemia and decreasing its stimulation of β-oxidation and ROS generation. Increase ROS generation potentially increase cytokine synthesis and release in certain organs (Figure 2).

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