MINI REVIEW

Mechanisms of hepatitis C virus-related insulin resistance

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Summary The hepatitis C virus (HCV) infection has been shown to have direct and/or indirect effects on glucose metabolism, leading to insulin resistance and, in predisposed individuals, type 2 diabetes. This is supported by several experimental, clinical and epidemiological data. The detailed molecular events leading to insulin resistance in HCV-infected patients are unclear. HCV infects primarily the liver and, to a very minor extent, mononuclear cells. Direct interactions between HCV products and the hepatocyte insulin signaling pathway have been reported by several authors. However, recent evidence supports the existence of a significant extrahepatic component of HCV-induced insulin resistance. Thus, the molecular pathogenesis of glucose metabolism disturbances observed in hepatitis C is much more complex than expected. The clinical management of such condition remains empirical.

Introduction

Hepatitis C virus (HCV) infection is a major cause of chronic progressive liver disease, including its long-term sequelae, i.e. cirrhosis and hepatocellular carcinoma [1]. Although some pathological features, such as steatosis, suggest a direct effect of HCV on cellular constituents, most liver damage is considered as being mediated by the host immune response [2]. This results in mononuclear infiltration of the liver parenchyma, leading to hepatocyte necrosis and progressive deposition of fibrotic tissue, in a typical wound-healing process [3]. However, the pathophysiology of hepatitis C must consider also some additional, clinically significant interactions between HCV and the host cell machinery, which may impact on HCV-related morbidity and mortality. It is well established that HCV perturbs the glucose metabolism, leading to insulin resistance and, in predisposed individuals, type 2 diabetes [4]. These alterations may lead to all common sequelae of diabetes, and, in addition, to accelerated fibrogenesis, increased incidence of hepatocellular carcinoma and impaired response to treatment with interferon alpha (IFN-α) [4]. Thus, the knowledge of the molecular pathways involved in the pathogenesis of insulin resistance in HCV infection is of paramount importance to determine its appropriate management.

Insulin signaling

The binding of insulin to its receptor in the plasma membrane of the cell triggers a complex cascade of downstream
HCV and insulin resistance

Figure 1 Schematic, simplified representation of the pathways leading to control of glucose metabolism via insulin signaling in hepatocytes. Some mechanisms of inhibition of the insulin signal transduction are also indicated. For explanations, please refer to the text. IR: insulin receptor; IRS: insulin receptor substrate; PI3K: phosphoinositide 3-kinase; PIP2: phosphatidylinositol diphosphate; PIP3: phosphatidylinositol triphosphate; PDK1: phosphoinositide dependent kinase 1; SOCS: suppressor of cytokine signaling; mTOR: mammalian target of rapamycin; mTORC2: mTOR complex 2; PTEN: phosphatase and tensin homolog; SHIP2: SH2-containing phosphoinositide 5'-phosphatase 2; PKC: protein kinase C; JNK: c-Jun N-terminal kinase; PP2A: protein phosphatase 2A.

signaling events (Fig. 1) [5]. The insulin receptor (IR) is a heterodimeric complex consisting of two α-subunits and two β-subunits with tyrosine kinase activity. Insulin binding to the α-subunits determines the β-subunits to transphosphorylate each other, increasing their kinase activity. Several IR substrates (IRS) have been described, but only IRS-1 and IRS-2 are relevant to hepatocyte signaling. IRSs contain several tyrosine residues that can be phosphorylated by the IR tyrosine kinase. Once phosphorylated, IRSs function as docking molecules for proteins containing an src homology region 2 (SH2) domain, such as the phosphatidylinositol 3-kinase (PI3K), activating them. PI3K is a heterodimer, consisting of a p110 catalytic subunit and a regulatory subunit: once activated, it phosphorylates the phosphoinositides at their 3-position to produce phosphoinositide 3-phosphates (PIPs). These molecules firstly activate the PI-dependent kinase 1 (PDK1) and then recruit the serine/threonine kinase Akt (also known as protein kinase B, PKB) to the plasma membrane. In order to be activated, Akt must be phosphorylated twice: first, by the mammalian target of rapamycin (mTOR) complex 2 at the serine 473, and then by the activated PDK1 at its threonine 308.

The protein kinase Akt/PKB is key effector of insulin action. In the liver, Akt prevents the transcription factor FoxO1 from entering the nucleus and activating genes that control gluconeogenesis, like the phosphoenolpyruvate carboxykinase and the glucose 6-phosphatase. In addition, Akt inactivates the glycogen synthase kinase 3 and allows for the persisting localization of glucose transporters at the plasma membrane, leading to increased glycogen synthesis and glucose uptake.

The lipogenic effects of insulin proceed also through the activation of the PI3K/Akt pathway. Insulin-stimulated lipogenesis is mediated by the transcription factor sterol regulatory element–binding protein (SREBP)-1c, although the full details of this are still unclear. The SREBPs family consists of three transcription factors: SREBP-1c is the dominant isoform in liver and adipose tissue, where it activates the fatty acid synthesis. Its regulation is complex and occurs at the transcriptional and posttranslational levels. Insulin seems to activate the transcription factor, liver X receptor (LXR), which is known to bind to the SREBP-1c promoter, thus activating its transcription. However, recent evidence suggests that also the mTOR complex 1 is required for the insulin-stimulated induction of SREBP-1c [6]. Akt activates mTOR by phosphorylating and inhibiting TSC2, an mTOR inhibitor. The mTOR is an important target of activated Akt, and it is not only involved in control of lipogenesis, but also in protein synthesis regulation.

Finally, another major pathway activated by insulin involves the mitogen-activated protein kinase (MAPK). This pathway is triggered by the IR-mediated tyrosine phosphorylation of IRS proteins, Gab1, and Shc, and is independent of PI3K. The MAPK pathway is associated with the cell growth effects of insulin.

Several factors may modulate/suppress insulin signaling, and their activation may lead to insulin resistance: protein tyrosine phosphatases (PTP) Shp1 and Shp2 may dephosphorylate IRSs [7], lipid phosphatases such as SH2-containing phosphoinositide 5'-phosphatase 2 (SHIP2) and the phosphatase and tensin homolog (PTEN) dephosphorylate PIPs [8], while the suppressors of cytokine signaling (SOCS) promote IRSs degradation [9]. Some kinases, including the mTOR substrate p70 ribosomal S6 kinase (p70S6K), the protein kinase C (PKC) and the c-Jun N-terminal kinases (JNK), induce insulin resistance through phosphorylation of serine residues of IRSs, which inactivates them [10].

HCV infection causes insulin resistance

Several epidemiological, clinical and experimental observations have provided convincing evidence that HCV plays a direct role in altering glucose metabolism, leading to insulin
Mechanisms of HCV-induced insulin resistance

Experimental data suggest a direct interference of HCV with the insulin signaling pathway. In an early study, fresh liver samples obtained from 42 nonobese, nondiabetic chronic hepatitis C patients and 10 non-HCV-infected subjects, matched for age and BMI, were incubated in vitro with hepatitis C patients and 10 non-HCV-infected subjects, samples obtained from 42 nonobese, nondiabetic chronic hepatitis C patients and 10 non-HCV-infected subjects, matched for age and BMI, were incubated in vitro with hepatitis C patients and 10 non-HCV-infected subjects, matched for age and BMI, were incubated in vitro with hepatitis C patients and 10 non-HCV-infected subjects, matched for age and BMI, were incubated in vitro with hepatitis C patients and 10 non-HCV-infected subjects, matched for age and BMI, were incubated in vitro with hepatitis C patients and 10 non-HCV-infected subjects, matched for age and BMI, were incubated in vitro with hepatitis C patients and 10 non-HCV-infected subjects, matched for age and BMI, were incubated in vitro with hepatitis C patients and 10 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resistance does not seem to be mediated by adipokines or pro-inflammatory cytokines.

Interestingly, recent evidence obtained by combining the use of euglycemic hyperinsulinemic clamp, infusion of labeled tracers and indirect calorimetry, shows that HCV infection is associated with a substantial peripheral component of the total insulin resistance [27,41]. Since HCV infects primarily the liver, these results raise the issue of the crosstalk between the liver and extrahepatic tissues involved in the glucose homeostasis, i.e. the striated muscle or the adipose tissue. Currently, most—if not all—of the extrahepatic insulin resistance seems to originate from muscles, since the adipose tissue retain the sensitivity to insulin when lipolysis is measured at the time of the euglycemic hyperinsulinemic clamp [41]. The circulating mediators of these effects are currently unknown.

Has our knowledge on the mechanisms of HCV-induced insulin resistance modified patients’ management?

Insulin resistance and diabetes have significant clinical consequences on chronic hepatitis C: (i) accelerated fibrogenesis [15,16,42—45], (ii) increased incidence of hepatocellular carcinoma [46,47] and (iii) reduced virological response to IFN-α-based therapy [19,45,48,49]. Thus, to unravel the mechanisms of insulin resistance induced by HCV is of paramount clinical importance. However, all approaches attempted so far have been empirical, i.e. using lifestyle measures and insulin sensitizers already in use in non-HCV-related insulin resistance and diabetes. This is partly due to the lack of SOCS inhibitors for clinical use, and to the fact that there is little, inconclusive evidence supporting the use of etanercept and/or infliximab (two TNF-α inhibitors) for correcting metabolic disturbances [50—53]. A single study proposing lifestyle changes was able to reduce insulin resistance and liver fibrosis in a small cohort of chronic hepatitis C patients [54]. The effects of such measures on the response to antiviral therapy were not assessed. The data reported in four independent studies using different schedules containing pioglitazone added to the pegylated IFN-α/ribavirin combination [55—58] fell short of demonstrating the efficacy of this insulin sensitizer on the virological response rate, although insulin resistance was reduced. The only study that used metformin has shown only a marginal, insignificant increase of the sustained virological response rate, together with an amelioration of the metabolic parameters [59].

In conclusion, HCV seems to induce insulin resistance via direct and indirect mechanisms. The knowledge of the molecular interactions underlying these effects is still very poor, and does not allow implementing mechanistic approaches to patients’ management.

Conflict of interest statement

The author confirms the absence of conflicts of interest related to the work presented here.

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