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Role of Resistin in Type 2 Diabetes Mellitus and Obesity in HHcy-Patients. Opposite Effects of Intermedin in Experimental Models

Federico Cacciapuoti1* and Fulvio Cacciapuoti2

[1]*Department of Internal Medicine, "L. Vanvitelli" University, Italy*

[2]*Cardiology and ICU, "V. Monaldi" Hospital, Italy*

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***Corresponding author:** Federico Cacciapuoti, Department of Internal Medicine, L. Vanvitelli" University, Naples, Italy

Abstract

Increased homocysteine serum levels (HHcy) cause the over-expression of Resistin, that yields the inflammation of adipocytes by some inflammatory cytokines, responsible of obesity, and insulin resistance often evolving towards type 2 diabetes mellitus and some cardiovascular diseases. Contrarily to Resistin, Intermedin of the calcitonin family, ameliorates HHcy-induced inflammation of adipose tissue, favoring the weight loss and the insulin sensitivity. The anti-inflammatory effects on adipocytes developed by this peptide depend by a novel mechanism that balances the pro-inflammatory/anti-inflammatory cytokines ratio, synthesized such as M1/M2 ratio. Insulin sensitivity and weight loss were obtained in mice treated with Intermedin. In the future, Intermedin administration could be used for type 2 diabetes mellitus and overweight treatment in humans too. But further studies are requested to evaluate that.

Keywords: Hyperhomocysteinemia; Type 2 diabetes mellitus; Adipocytes; Obesity; Resistin; Intermedin

Abbreviations: HHcy: HyperHomocysteinemia; T2DM: Type 2 Diabetes Mellitus; ERS: Endothelial Reticulum Stress; TNF: Tumor Necrosis Factor; IL-6: InterLeukin-6P; JNK: c-Jun-N-Kinase; Akt: Activity-Threonine Kinase; Hcy: Homocysteine; Met: Methionine; MTHFR: Methilene-Tetra-Hydro-Folate Reductase; CBS: Cystationine-Beta-Synthase; CSE: Cystationine-Gamma-Lyase; ROS: Reactive Oxygen Species; LDL: Low Density Lipoprotein; IMD: Intermedin; AM2: Adreno Medullin 2; AMP: Adenyl Mono Phosfate; AMPK: Activation Protein Kinase; PKA: Protein Kinase Activationue; WAT: White Adipose Tissue

Introduction

Some evidence suggest that hyperhomocysteinemia (HHcy) can favor insulin resistance, responsible for increased glycemic serum levels. That can provoke pre-diabetes or type 2 diabetes mellitus (T2DM) and/or other numerous pathological conditions, such as obesity and some cardiovascular diseases é [1-4]. Li et al. [4] hypothesized that, in experimental hyper-homocysteinemic-models, insulin resistance was obtained through the expression of Resistin from adipose tissue via endothelial reticulum stress (ERS). In detail, HHcy causes an inflammatory reaction of adipocytes, responsible to produce some pro-inflammatory cytokines, such as tumor necrosis factor-alfa (TNF-alfa), and interleukin (IL-6). In turn, these activate c-jun N terminal-kinase (JNK) which inhibits serine/threonine protein-kinase (Akt) activity that impairs insulin signaling pathway, causing the over-expression of Resistin. On the other hand, Resistin overexpression, with consequent insulin resistance, represents a frequent cause of both T2DM and obesity [4-7].

Homocysteine

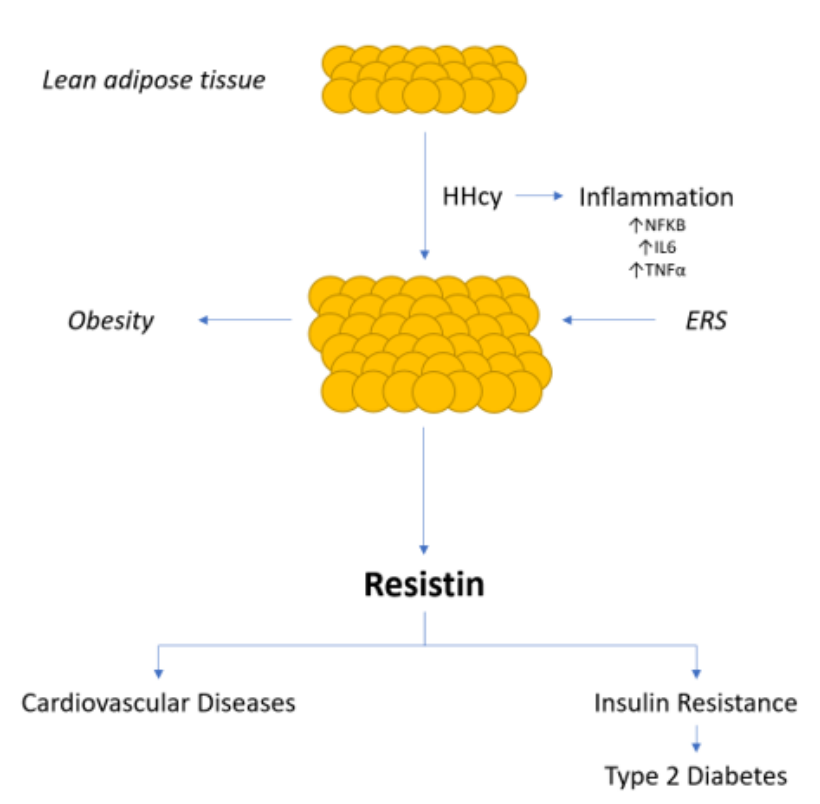
Homocysteine (Hcy) is an amino acid formed during the metabolism of Methionine (MET). Its storage (HHcy) depends on the defective re-methylation and/or trans-sulfuration pathways [8]. Particularly, re-methylation route favors Met re-synthesis. On the contrary, trans-sulfuration pathway concerns the further metabolism of Hcy until its final product (cysteine). Both pathways require some enzymes, respectively for Met synthesis (MTHFR) and cysteine production (CBS, CSE) [9]. But these enzymes require, to operate, some coenzymes, as folic acid, vitamin B12 (MTHFR) and vitamin B6 (CBS, CSE). Their deficiency induces HHcy [10], that besides acts as a potent inflammatory factor of adipocytes [11]. Previously, it was demonstrated that Hcy is able

to induce expression of proinflammatory factors by the mediation of oxidative stress [12]. Thus, HHcy can be considered a chronic inflammatory condition [13]. On the other hand, this inflammation of adipocytes causes the Resistin expression through some pro-inflammatory cytokines [2].

Resistin

HHcy, a cysteine rich peptide hormone, may promote insulin resistance, through the Resistin expression from adipocytes in rodents, via the activation of the inflammatory pathways. In humans, contrarily to the rodents, the source of Resistin is mainly represented by macrophages, that are similar to adipocytes [14]. Resistin over-expression can be obtained in HHcy-patients through the generation of Reactive Oxygen Species (ROS), that weaken the function of insulin secreting cells. Resistin works by helping the body's cells to absorb glucose. In turn, the body converts this into fat, inducing obesity, especially of the visceral type [15].

Resistin is a hormone involved in the pathogenesis of insulin resistance and may link T2DM with obesity through some inflammatory markers [16] (Figure 1). But, Resistin is also associated to atherosclerosis, endothelial dysfunction, some cardiovascular disease, alcoholic fatty liver disease and inflammation [17-19]. In addition, Resistin is responsible for high levels of low-density lipoproteins (LDL) and favors the accumulation of these in the arteries, with consequent atherosclerosis [20]. Its role in pro-inflammatory processes has been demonstrated in several studies [21,22]. High levels of Resistin have also been associated with other chronic inflammatory diseases, such as rheumatoid arthritis, but its role in systemic lupus erythematous is controversial [23,24]. In addition, Resistin, and the derived insulin resistance, can act as anti-apoptoic, pro-angiogenic molecule with pro-metastatic activity and regulate metabolic activities in cancer's cells [25-27].



HHcy: Hyperhomocysteinemia; ERS: Endothelial Reticulum Stress; T2DM: Type 2 Diabetes Mellitus

Figure 1: Mechanism through HHcy provokes adipocytes' inflammation (obesity). That causes Resistin overexpression, responsible for insulin resistance (favoring T2DM) and some cardiovascular diseases.

Intermedin

Contrarily to Resistin, Intermedin (IMD), also known as adrenomedullin 2 (AM2), a calcitonin family peptide, acts with opposite effects of Resistin on insulin resistance and obesity [28,29]. Referring to HHcy, it was demonstrated that IMD ameliorates HHcy-induced chronic inflammation in adipose tissue and improves insulin sensitivity in experimental models. In addition, IMD protects the myocardium from ischemia-reperfusion injury, by inhibiting oxidative stress [30]. As previously affirmed HHcy promotes the inflammatory state of adipocytes, through the Resistin expression. A novel mechanism was proposed by Pang et

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al. for Hcy-induced macrophages' inflammation. That consists in the prevalence of M1/M2 ratio (M1 consists of pro-inflammatory cytokines, as IL-1, IL-6, TNF-alfa; M2 includes anti-inflammatory cytokines, such as IL-1, IL-4, IL-6, IL-10, IL-11, IL-13). The impaired M1/M2 ratio favors the inflammation of macrophages causing Resistin expression [31]. Contrarily to this mechanism, the over-expression of IMD balances the M1/M2 ratio, reducing the inflammatory reaction of adipocytes and inhibits insulin resistance [32] (Figure 2). This effect happens by the activation of AMP-activated protein kinase (AMPK). That stimulates glucose uptake in skeletal muscle and reduces hepatic glucose production [33]. In addition, IMD can attenuate inflammation in adipose tissue of obese rats, through receptor-mediated cAMP-dependent protein kinase (PKA) activation receptor [34].

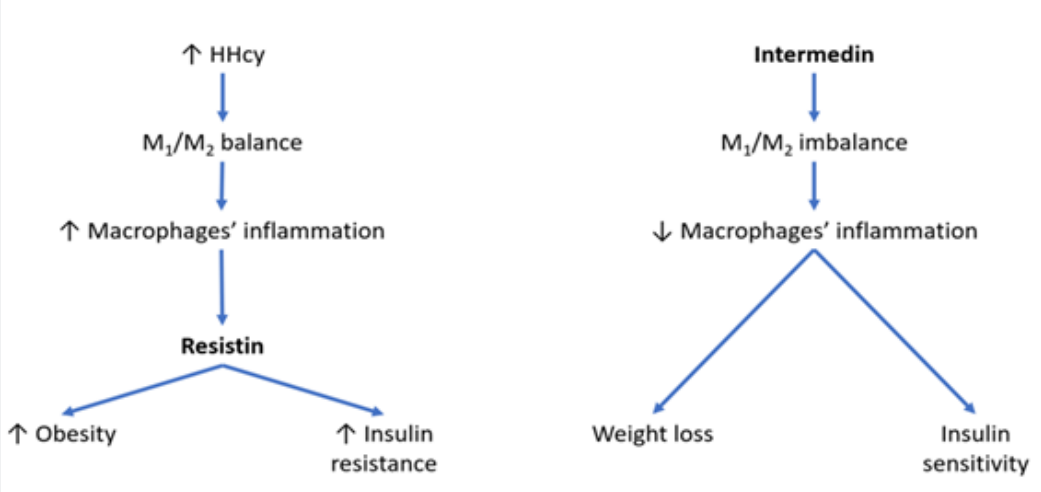

Figure 2: left Novel mechanism through HHcy causes both obesity and insulin resistance. Right-Opposite effects of Intermedin on overweight and insulin senstivity.

In summary, whereas HHcy favors the adipocytes-inflammation for Resistin expression, in turn, induces insulin resistance and obesity. The M1/M2 ratio imbalance happening in macrophages through IMD, favours that [35]. For this novel mechanism, IMD administration could likely represent a new therapeutic strategy to antagonize insulin resistance, T2DM, obesity and other cardio-metabolic diseases [36]. Concerning the obesity, it was observed that, the IMD infusion (300 ng/Kg x hour) in obese rats attenuates inflammation in white adipose tissue (WAT). This effect was obtained through the mitogen-activated protein kinase (MAPK) and nuclear factor kB (NF-kB) activation by the receptor PKA pathway. The WAT activation of obese rats decreased body weight and results to be associated with anorexigenic effects [37] and inhibition of gastric emptying [38]. Consequentially, IMD could be interesting as a potential target for the treatment of insulin resistance and obesity in humans too, even if several other investigations both in animal models and in humans are requested [34].

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