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Review

Rho kinase, a potential target in the treatment of metabolic syndrome

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ABSTRACT

Introduction: Metabolic syndrome is a health issue which is recognized due to its insulin resistance, central obesity, dyslipidemia, and hypertension. Since the Rho family of GTPases are involved in several cellular mechanisms, it is believed they might be involved in different aspects of metabolic syndrome. We conducted a search of some databases such as PubMed for articles and reviews published between 1997 and 2017, with different keywords including "metabolic syndrome", "rho kinase", "dyslipidemia", "hypertension", "central obesity", "insulin resistance" and the connectors AND or OR. Studies revealed that Rho kinase over-activity leads to cardiovascular diseases, such as hypertension and dyslipidemia, through decreasing NO production. Since NO has beneficial effects on lipid metabolism through activation of hepatic sterol regulatory element-binding protein (SREBP)-2, its inhibition can contribute to higher levels of LDL cholesterol and also results in increased myosin light chain activation with vasoconstriction. Moreover, Rho kinase enhances insulin substrate 1 (IRS-1) phosphorylation, leading to the development of insulin resistance.

Conclusion: In conclusion, the present review demonstrates that upregulated Rho kinase activity involves in the pathogenesis of all aspects of metabolic syndrome. Taken together, these results implicate the therapeutic potential of the Rho-kinase pathway as an important new target in medicine.

1. Introduction

Metabolic syndrome (MetS) is a complicated abnormality which is a result of unhealthy diet and low physical activity. It is well known due to its insulin resistance, central obesity, dyslipidemia, and hypertension. Reaven was the first one who pointed out the importance of syndrome as a bundle of abnormalities, with insulin resistance as the core pathophysiological feature of which he labeled "syndrome X". However, Reaven did not include obesity, which seems to be one of the key factors of metabolic syndrome [1–3]. Here we first provide the most commonly used definitions for MetS which are introduced by the world health organization (WHO), the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III), the International Diabetes Federation (IDF), and the Joint Interim Societies (JIS) [4] and then introduce one of the important cell regulators that might be involved in the pathogenesis of the disease(Fig. 1).

Based on the National Cholesterol Education Program (NCEP) criteria, diagnosis of the metabolic syndrome needs at least three of the following factors to be present: abdominal obesity: waist circumference > 102 cm in men and > 89 cm in women (in case of body mass index (BMI) > 30 kg/m2, central obesity can be assumed instead of measuring waist circumference), raised plasma triacylglycerol (TG) ≥150 mg/dL, reduced high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL in men or < 50 mg/dL in women, raised blood pressure

Abbreviations: WHO, World Health Organization; NCEP-ATP III, the National Cholesterol Education Program Adult Treatment Panel III; IDF, the International Diabetes Federation; JIS, the Joint Interim Societies; NCEP, National Cholesterol Education Program; MetS, metabolic syndrome; BMI, body mass index; TG, triacylglycerol; HDL-C, high density lipoprotein – cholesterol; GTP, guanosine triphosphate; eNOS, endothelial nitric oxide; NO, nitric oxide; ROCK, rho associated kinase; IRS, insulin receptor substance; PI3K, phosphoinositide-3- kinase; AKT, protein kinase B (PKB); Glut, glucose transporter; IR, insulin receptor; PTP, protein tyrosine phosphate; AGE, advanced glycation end protein; ROS, reactive oxygen species; LDL, low density lipoprotein; FFA, free fatty acid; PKC, protein kinase C; NOX-1, NADPH oxidase 1; NADPH, nicotinamide adenine dinucleotide phosphate; VSM, vascular smooth muscle; AMPK, 5 AMP activated kinase; UCP-1, uncoupling protein-1; ASCVD, atherosclerotic cardiovascular disease; OXLDL, oxidized LDL; PPAR, peroxisome proliferator activated receptor; SREBP, sterol regulatory element binding protein; PKG, protein kinase G; PKB, protein kinase B; MLC, myosin light chain; EC, endothelial cells; CypA, cyclophyline A; LVDCC, L-type voltage dependent calcium channel; SAH, subarachnoid hemorrhage; PAI-1, plasminogen activator inhibitor-1; RASMC, rat aortic smooth muscle cells; Iv, intravenous; MLCP, myosine light chain phosphatase; MCP-1, monocyte chemoattractant protein-1; TNF-α, tumor necrosis factor

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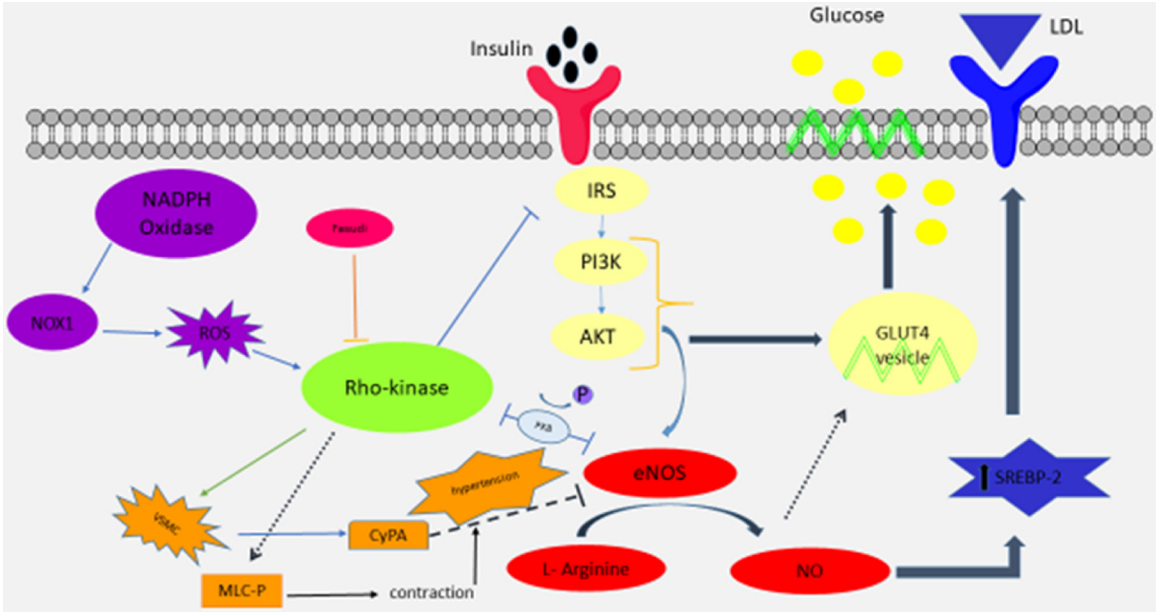

Fig. 1. Rho kinase involvement in metabolic syndrome pathogenesis. Rho kinase interacts with lipid metabolism mostly through inactivation of hepatic SREBP. This is mainly a result of eNOS inactivation. This also results in reduced VSMC relaxation, which can further contribute to hypertension. Moreover, Rho kinase activation results in CYPA secretion from VSMC. This factor is an inhibitory stimulus for eNOS, as well. At glucose transportation level Rho kinase can IRS-1phosphorylation. This results in insulin resistance. eNOS counterbalance with Rho kinase is also a part of non-insulin mediated pathway in glucose transport. This is mostly due to NO effect on GLUT4 translocation to the cell membrane, which enhances glucose transport. Furthermore, obesity as an inflammatory state can result in activation of NADPH derived NOX1, which causes ROS generation. This ends in Rho kinase activation, which might indicate the underlying cause of insulin resistance in the obese population.Abbreviations : NADPH, nicotinamide adenine dinucleotide phosphate; NOX1, NADPH Oxidase 1; ROS, reactive oxygen species; VSMC, vascular smooth muscle cell; MLC-P, Myosin-light-chain phosphatase; CYPA, cyclophilin A; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; SREBP, sterol regulatory element binding protein; LDL, low density lipoprotein; IRS, insulin receptor substance; PI3K, phosphatidylinositide 3-kinases; AKT, Protein kinase B; GLUT4, Glucose transporter type 4.

≥130/85 mmHg, and fasting plasma glucose of 110–125 mg/dL. While there is still no available serological marker for detection of obesity, it is now recognized as an established risk factor for type 2 diabetes mellitus and cardiovascular diseases (CVDs) and increases their incidence by approximately five and three folds, respectively [5,6].

The Rho family of GTPases, which are belonged to RAS superfamily, are one of the key regulators of cell behavior [7]. It has commonly been assumed that Rho-associated kinase or ROCK, mediates the downstream signaling of the small guanosine triphosphate-binding protein, Rho, on the actin cytoskeleton. Hence, it is involved in actin-myosin contractions [8]. It is present in inactive GDP-bound and active GTP-bound [9] (Table 1).

Several factors can trigger Rho kinase activation. Factors such as angiotensin II, thrombin, and high levels of glucose in endothelial cells or smooth muscle cells [10]. It is widely associated with many signaling pathways including regulation of cell contraction, cell polarity, gene transcription, G1 cell cycle progression, microtubule movement, vesicular transport pathways and a diverse range of enzymatic activities [7]. It is involved in lipid metabolism within its enzymatic activity [11]. Moreover, it is believed that ROCK interaction with endothelial nitric oxide synthase (eNOS) at expression and phosphorylation level is one of the most important mechanisms by which ROCK mediates endothelial injury [12].

The two isoforms of ROCK, including ROCK1 and ROCK2, contain 33 exons and are located on chromosome 18 and 2 in humans [13]. While they share some similarities at distribution level there are some differences in their expression pattern in some tissues. ROCK2 has a high level of expression in the brain while it is weakly expressed in lung. On the other hand, ROCK1 is expressed at high levels in the heart, lung, skeletal muscle, kidney, thymus, blood and pancreas, at medium levels in placenta and liver, and hardly at all in the brain [13,14].

The two C and N terminal on the structure of the enzyme is essential for catalytic activity. The ROCK kinase domains are located in the N-terminal region, followed by a coiled coil region with a Rho binding site and a PH-like region at the end of C-terminal. Several studies revealed that C-terminal region is a negative regulatory part of Rho kinase activity and deleting this area results in activation of either kinase *in vitro* and *in vivo*. It has been demonstrated that Rho binding domain at C-terminal and pH domains bind to ROCK kinase domain at N-terminal and therefore inactivate enzyme to prepare it for a resting state. On the other hand, GTP interaction with ROCK kinase domain interrupts the C-terminal bound at the area and results in enzyme activation. Rho kinase inhibitors insert their inhibitory effects in a competitive manner with ATP at binding site of ROCK kinase domain [13–15].

Since the enzyme is believed to be involved in different aspects of metabolic syndrome, this review is designed to focus on Rho kinase role and its multiple mechanisms involved in the pathogenesis of metabolic syndrome.

We conducted a search of some databases such as PubMed, Web of Science, Scopus and Science direct for articles and reviews published between 1997 and 2017, with different keywords including “metabolic syndrome”, “Rho kinase”, and the names of different aspects of metabolic syndrome itself such as: “dyslipidemia,” hypertension”,” central obesity”,” insulin resistance” and the connectors AND or OR. We also used the terms “mechanism” and “physiopathology”. The results are categorized into three groups: Insulin resistance and obesity, dyslipidemia and hypertension.

1.1. Insulin resistance and obesity

Obesity has always been an important issue due to its associated complications such as metabolic dysfunction, fasting hyperglycemia, insulin resistance and dyslipidemia, all of which cause a great concern and contribute to the morbidity of obesity [16]. There is a well-known correlation between insulin resistance and type 2 diabetes, which is mainly a result of insulin tissues inability to respond to the insulin that