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Perspective

Effects of Nebivolol Treatment on Glucose and Lipids Metabolism

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Abstract

The metabolic syndrome is defined as a set of physiological alterations which includes impaired glucose tolerance, dyslipidemia and hypertension. There are three generations of β-adrenergic antagonists differentiated by selectivity and affinity of the three β-adrenergic receptors. The classic β-blockers have been related to metabolic alterations as weight gain, increase of insulin resistance, which turn its use limited in the clinic. On the other hand, nebivolol is a third generation β1-adrenergic receptor antagonist that must be positively used in patients with metabolic syndrome. This drug does not affect the body weight and is able to produce reduction of oxidative stress, leading to decrease of insuline resistance and increase of insuline sensivity. Nebivolol is also able to decrease triglyceride and cholesterol serum levels, lowering the risk of cardiovascular impairment.

Keywords: Metabolic syndrome; Glucose metabolism; Lipid metabolism; β-blockres; nebivolol

Metabolic Syndrome

The metabolic syndrome is defined as a set of physiological alterations which includes impaired glucose tolerance, dyslipidemia and hypertension. In this sense, metabolic syndrome is associated to increased risk of cardiovascular disease and Chronic Kidney Disease (CKD) in general group of patients and mainly in carriers of type 2 diabetes [1]. In a variety of clinical researches, high levels of serum insulin are associated with increased blood pressure and a great risk of hypertension development. Insulin resistance in parallel to high blood pressures is a result of impaired insulin metabolic signaling which consequently causes reduction of glucose transport and reduced non oxidative glucose metabolism in insulin-sensitive tissues such as skeletal muscle. Thus this abnormal response of insulin intracellular signaling is characterized by alteration of Insulin Receptor Substrate 1 (IRS1) link with the regulatory subunit p85 of Phosphoinositol 3-Kinase (PI3K) and protein kinase B activation [2].

It is also important to mention that there is a variety of evidences that demonstrates that oxidative stress and inflammation must be related to the development of metabolic syndrome [1]. In this sense, some previous studies suggested that regulation of adipose tissue may represent an important link between increased insulin resistance, hypertension and obesity, all key factors in a range of metabolic alterations [3].

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Pharmacology of three generation β -blockers

There are three generations of β-adrenergic antagonists differentiated by selectivity and affinity of the three β-adrenergic receptors. Representative of the first generation, propranolol has the non-selective antagonist effect β1 and β2-adrenergic receptors. In relation to the second generation representatives, among them practolol, atenolol and metoprolol present selective antagonism of the β1-adrenergic receptor [4].

The third generation representatives, labetalol, carvedilol and nebivolol are praised as β-adrenergic antagonists and vasodilators. Regarding labetalol and carvedilol, in addition to the β1-drenergic antagonist effect, they also block the α1-adrenergic receptor characterizing its vascular relaxing effect. Nebivolol in turn is the most selective β1-adrenergic receptor antagonist that also has the β3-adrenergic receptor agonist effect, which activates the eNOS enzyme, leading to the increase of NO levels and vasodilation [4].

Classic β-blockers and metabolic syndrome

The traditional antagonists of β-adrenergic receptors, including propranol (first generation) and metoprolol and atenolol (second generation) represent one of the most widely used drugs for the treatment of cardiovascular disease. Although these classic β-blockers has been related to metabolic alterations as weight gain, increase of insulin resistance, which turn its use limited in the clinic [5]. In this sense, β-adrenergic receptors antagonists may increase the risk of metabolic syndrome including the development of diabetes, which is associated with a reduced transport of glucose into peripheral tissues and increased hemoglobin A1c (HcA1c) levels and mean plasma glucose, dyslipidemia related to obesity and unbalance of the lipid profile [6,7].

Effect of treatment with nebivolol on glucose metabolism

In a study developed by Ayers et al. [8], it was observed that patients which adhered treatment with metoprolol, 100 mg, during 12 weeks, presented increase of Plasminogen Activator Inhibitor-1 (PAI-1) expression, associated with reduced insulin resistance and these metabolic impairments were not observed in patients treated

with 5 mg of nebivolol, during 12 weeks. These results suggest that nebivolol maintenance of PAI-1 was able to control the development if insulin resistance and this effect must be related to nebivolol-induced increased activity of Nitric Oxide Sythase (NOS).

The oxidative stress must cause the activation of redox-sensitive serine kinases which induce serine phosphorylation and ubiquitination of Insulin Receptor Substrate 1 (IRS-1), that cause its degradation [2]. Thus, Manrique et al. [2] used male transgenic TG (mRen2) 27 (Ren2) rats (6-9 weeks of age) and age-matched Sprague-Dawley (SD) which were randomly included in placebo (Ren2-C and SD-C) or nebivolol group of treatment. During 21 days, Ren2-N and SD- N rats received 10 mg/kg/d of nebivolol released *via* an implanted osmotic minipump. Thus this research observed that the treatment with nebivolol prevented the reduced expression of IRS-1 with consequently improve of insulin resistance in parallel to increased levels of NO and decreased activity of NADPH oxidize in skeletal muscle. Similar results were observed by Ozyıldız et al. [6] which demonstrated that 5 mg-daily dose of nebivolol in newly diagnosed patients with hypertension, during 4 months improved glucose and insulin plasma levels, associated to reduced insulin resistance.

It is also important to mention that diabetic patients present higher risk of exhibiting unbalance of coagulation state characterized by increased levels of PAI-1 and also a rise of vascular inflammation [9]. Thus, Toblli et al. [9] observed that diabetic and obese mice treated with nebivolol 10 mg/kg/day, during 6 months was able to reduce aortic expression of adhesion molecules, such as VCAM-1 and PECAM-1, and also a reduction in platelet aggregation, which demonstrate a great effect of this third generation β-blocker in a prothrombosis state. In the same line, Whang et al. [10] demonstrated that diabetic and obese mice treated with nebivolol 10mg/kg/day during 6 months improved insulin plasma levels in parallel to increased insulin sensitivity. These responses were associated to improvement of renal function and structural integrity, showing that nebivolol prevented the evolution of diabetic nephropathy. These positive effects observed by third generation β-blocker must be related to its reduction of renal oxidative stress and lower expression of AMPK and p-AMPK (Thr172) which are involved on hyperglycemia-induced renal damage. On the other hand, NO plays protective effects on kidney structure and function. Thus Whang et al. [10] also demonstrated that nebivolol restored endothelial NOS (eNOS) activity and expression leading to vasodilatation and improvement of kidney perfusion.

Effect of treatment with nebivolol on lipids metabolism

The lipolisys may be induced by β3-adrenergic receptor activation in human visceral adipocytes and the resulting fat acids from brown tissue has been used for thermogenesis by uncoupling protein 1 (UCP-1) [11]. In the study developed by Bordichia et al. [11], the authors observed that a low concentration of L-nebivolol (10 nmol/l) caused significant lipolysis in subcutaneous and visceral adipocytes as observed in cells treated with BRL37344 (β3-adrenergic receptor agonist). The researchers also observed that this response was suppressed by a pretreatment with SR59230A (β3-adrenergic receptor antagonist), confirming the hypothesis that nebivolol-induced lipolysis is mediated by β3-adrenergic receptor. Then Bordichia et al. [11], also observed that L-nebivolol increased the expression of brown adipocytes genes UCP- 1, PPARγ coactivator-1α (PGC-1α) and the mitochondrial gene cytochrome c (CYCS), all mediated by β3-adrenergic receptor activation.

There are a variety of information's that demonstrate that patients with type 2 diabetes present impairment of mitochondrial glucose and fatty acid metabolism and mitochondrial loss in muscle and adipose tissue. It is also important to mention that mitochondrial biogenesis must improve these metabolic disruptions and its response is modulated by PGC-1α which activation depends of Calcium/Calmodulin-Dependent Protein Kinase IV (CaMKIV), AMP-Activated Protein Kinase (AMPK) and Nitric Oxide (NO). The higher expression of PGC-1α causes the transcription of important proteins as nuclear respiratory factors Nrf1 and Nrf2, which induce the higher expression of Tfam, which translocates into mitochondria and activates its biogenesis [12-14]. In this sense, Huang et al. [5] demonstrated that nebivolol is able to cause the increased expression of PGC-1a, Sirt3, Tfam and Nrf1 proteins, all involved in mitochondrial biogenesis. In parallel Huang et al. [5] also observed a raise of oxygen consumption and number of mitochondrial DNA copy which must plays an essential role in fatty oxidation [5].

Finally, Toblli et al. [9] showed that obese and type 2 diabetic mice treated with nebivolol (10 mg/kg/day), during 6 months, presented a reduced renal damage associated to lower serum levels of triglyceride and serum cholesterol. The authors also verified a decreased renal oxidative stress and inflammation which results on improvement of kidney function and structure. In the same line, Zhou et al. [15] also observed nebivolol-induced positive effects on lipid profile and reduction of vascular oxidative stress in diabetic and obese mice and these responses are mediated by eNOS-dependent increase of NO.

In summary, nebivolol is a β-blocker that must be positively used in patients with metabolic syndrome. This drug is able to produce reduction of oxidative stress, leading to decrease of insuline resistance and increase of insuline sensivity. Nebivolol is also able to decrease triglyceride and cholesterol serum levels, decreasing the risk of cardiovascular impairment.

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